Handbook

The MD Anderson Surgical Oncology Handbook

Sixth Edition

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Associate Editor
C. Denise Ching

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Wolters Kluwer

SIXTH EDITION

The MD Anderson Surgical Oncology Handbook

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To my family—Barbara, Rachel, and Jared—thank you for your unqualified love and never-ending support.

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PREFACE

It is difficult for me to fathom that it has been over 25 years since the first suggestion was floated to the surgical oncology fellows at the MD Anderson Cancer Center to consider organizing our philosophies and practices regarding the surgical treatment of cancer into an organized literary publication. It took 2 years to coerce several of us to undertake this project. Never in my wildest imagination did I imagine at that time, that this handbook would turn out to be the defining achievement in my academic career in surgical oncology. The handbook has been markedly more successful than any of us involved in that first edition in 1993 could ever have imagined. This is reflected in the over 33,000 units that have been sold over that time period. I am proud to have been afforded the privilege to be a part of this project from its inception and thereby, as a result, been able to contribute to the success of the handbook. As one of only two contributors involved in all six editions of *The Handbook*, I view that my most important role in the production of the handbook has been to keep the consistency of the original mission alive. That mission, "to document the philosophies . . . and outline basic management approaches based on our experience . . . at the MD Anderson Cancer Center," has been able to be consistently perpetuated through all six editions. Although the original intended target audience for the book was surgical house staff and surgical oncology trainees, we were surprised to learn even early in the first edition, that the appeal of the handbook ranged from medical students to academic faculty. We continue to aim for that same initial target audience but remain proud of the continued wide spectrum of appeal (including the "underground" use of the handbook at "other" major cancer centers). Additionally, as in the first edition, the overwhelming majority of the writing is done by the MD Anderson surgical oncology fellows with oversight by one of the surgical oncology specialized faculty—many of these faculty members were "fellow authors" in previous editions and have subsequently become internationally recognized experts in their respective fields.

Like all productive endeavors, the ability to achieve success is rarely the result of a single individual, but rather, more likely the culmination of the efforts of a large team of people. Certainly, the latter scenario is the situation responsible for this handbook. Most likely, this will be the last edition of *The Handbook* which I will have the privilege of being involved with. As the primary person responsible for continuity of the handbook I feel a responsibility for recognizing those individuals that have been instrumental in its success.

The initial concept of a handbook of surgical oncology was the brainstorm of the editorial staff of the Little, Brown and Company. It is only through their persistence, despite multiple initial rejections, that *The MD Anderson Surgical Oncology Handbook* was able to become a reality.

Acknowledgment must go to David Berger for having the insight and courage to realize the potential value of documenting our ideas and practices when the unanimous opinion of the other surgical oncology fellows was against the idea of creating a handbook. Although I wasn't sure that I agreed with him and I never imagined the handbook having anywhere near the level of success that it has achieved, I am certainly glad that he was able to persuade me to help him create the initial handbook.

Melissa Burkett, of the Department of Scientific Publications at MD Anderson has been involved, at some level, in all editions of *The Handbook*. It is her editorial skills which enabled the first edition to be readable and consistent despite the large number of initial authors who, as a group, were relatively inexperienced in the details of successfully writing and publishing a book.

A debt of gratitude goes to the surgical oncology fellows who have trained at the MD Anderson Cancer Center over this 25-year time period. The fellows have been the primary authors of *The Handbook* as well as the motivation for the continued pursuit of academic excellence in the department of surgical oncology.

Most important are the innumerable oncology patients who have occupied the inpatient and outpatient facilities of the MD Anderson Cancer Center over this time period. Their courageous spirit in each one of their battles against their cancer has been an inspiration for all of us providing care to continue to pursue an increased knowledge base in order to potentially provide improved care and surgical outcomes.

Six years have passed since the publication of the previous edition of *The MD Anderson Surgical Oncology Handbook*. During that time frame

there have been many advances in clinical options available and treatment algorithms. Every chapter in the current edition has been updated in an effort to capture all relevant advances in surgical oncologic care. It is my hope that this updated clinical information along with the new e-book format will make this current edition of *The Handbook* as relevant and useful as the previous editions have proven to be. As there are still many advances required before we officially win the “war on cancer” it is my sincere hope that someone will pick up the responsibility of continuing the tradition and relevance of the handbook in order to providing continuity to the practice of surgical oncology.

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1 Noninvasive Breast Cancer

Oluwadamilola M. Fayanju, Aysegul A. Sahin, and Kelly K. Hunt

INTRODUCTION

Ductal carcinoma in situ (DCIS) is noninvasive carcinoma of the breast and is defined as the proliferation of malignant epithelial cells confined to the mammary ducts and without evidence of invasion through the basement membrane. Because it is noninvasive, DCIS does not pose a risk of metastasis. Although previously considered a form of noninvasive carcinoma, lobular carcinoma in situ (LCIS) is now understood to be a pathologic marker of increased bilateral breast cancer risk. Atypical lobular hyperplasia (ALH) and LCIS are both forms of lobular neoplasia and, together with atypical ductal hyperplasia (ADH), represent proliferative nonmalignant breast lesions.

DUCTAL CARCINOMA IN SITU

Epidemiology

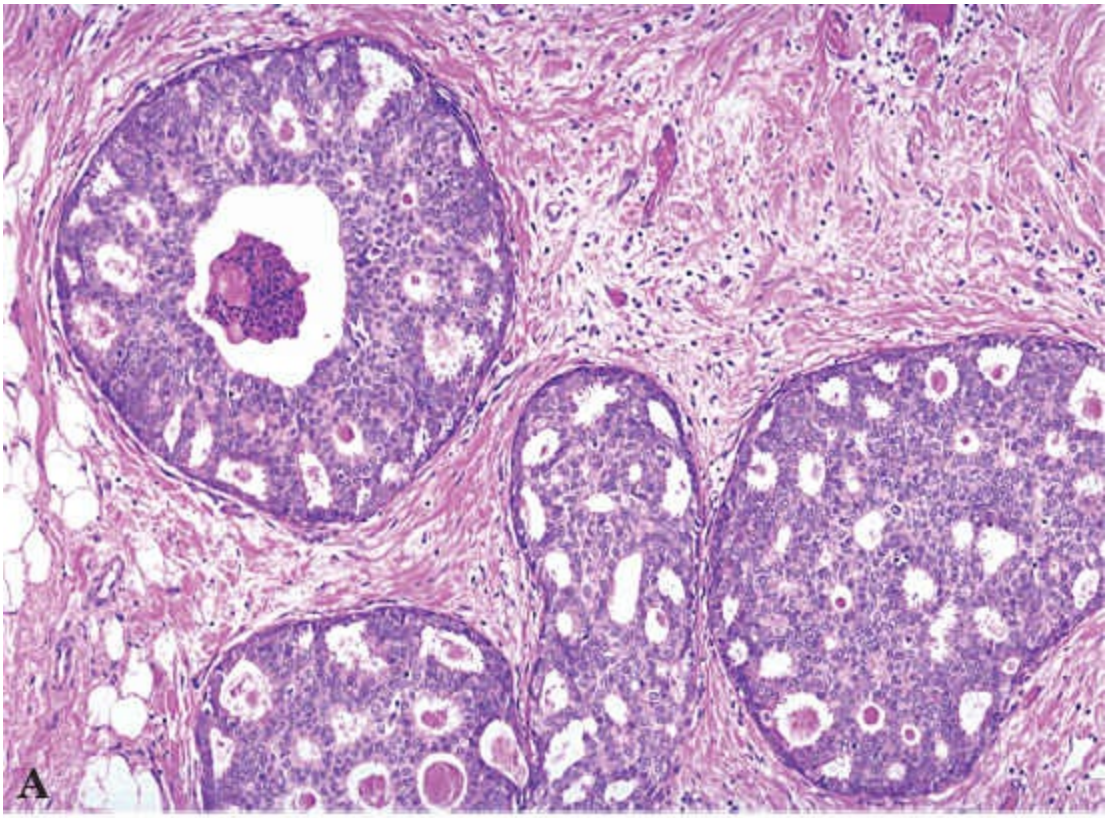
One in eight women (i.e., 12%) in the United States (US) will be diagnosed with breast cancer in her lifetime, and 20% to 25% of these newly diagnosed cases are DCIS. In 2016, an estimated 61,000 cases of DCIS were diagnosed in US. Widespread use of screening mammography has resulted in a 10-fold increase in the reported incidence of DCIS since the mid-1980s, but since 2003, the incidence of DCIS has declined in women age 50 years and older—possibly due to decreased use of hormone replacement therapy—while the incidence in women under 50 continues to increase. Approximately 1 in every 1,300 mammography examinations performed in US will lead to a diagnosis of DCIS, representing 17% to 34% of all mammographically detected breast cancers. Before the introduction of screening mammography, most cases of DCIS were not detected until a palpable mass formed, but today, 80% to 85% of DCIS cases are screen detected. The incidence of DCIS in autopsy studies is

higher than in the general population, suggesting that not all DCIS lesions become clinically significant and supporting concerns that most of the increase in DCIS incidence is due to the detection of nonaggressive subtypes that are unlikely to progress to invasive cancer.

The median age reported for patients with DCIS ranges from 47 to 63 years, similar to that reported for patients with invasive carcinoma. However, the age of peak incidence for DCIS—96.7 per 100,000 women—occurs between the ages of 65 and 69 years, which is younger than that for invasive breast cancer, for which peak incidence—453.1 per 100,000 women—occurs between the ages of 75 and 79 years. The frequency of first-degree relatives having breast cancer (i.e., 10% to 35%) as well as rates of deleterious mutations in the breast cancer–associated (BRCA) genes are the same for patients with DCIS as for women with invasive breast malignancies. Other risk factors for DCIS—including older age, proliferative breast disease, increased breast density, nulliparity, older age at primiparity, history of breast biopsy, early menarche, late menopause, long-term use of postmenopausal hormone replacement therapy, and elevated body mass index in postmenopausal women—are the same as those for invasive breast cancer, but in many instances, the association between a given characteristic and invasive cancer is stronger than the association between that characteristic and DCIS.

Pathology

DCIS is a proliferation of malignant cells that have not breached the ductal basement membrane. They arise from ductal epithelium in the region of the terminal ductal–lobular unit (TDLU). DCIS had previously been considered one stage in the continuum of histologic progression from ADH to invasive carcinoma. But, in fact, DCIS comprises a heterogeneous group of lesions with variable histologic architecture, molecular and cellular characteristics, and clinical behavior (Fig. 1.1). Malignant cells proliferate until the ductal lumen is obliterated, and there may be associated breakdown of the myoepithelial cell layer of the basement membrane surrounding the ductal lumen. DCIS has also been linked with changes in the surrounding stroma resulting in fibroblast proliferation, lymphocyte infiltration, and angiogenesis. Thus, although the process is poorly understood, most—but not all—invasive ductal carcinomas are believed to arise from DCIS, which is considered a nonobligate precursor of invasive breast carcinoma.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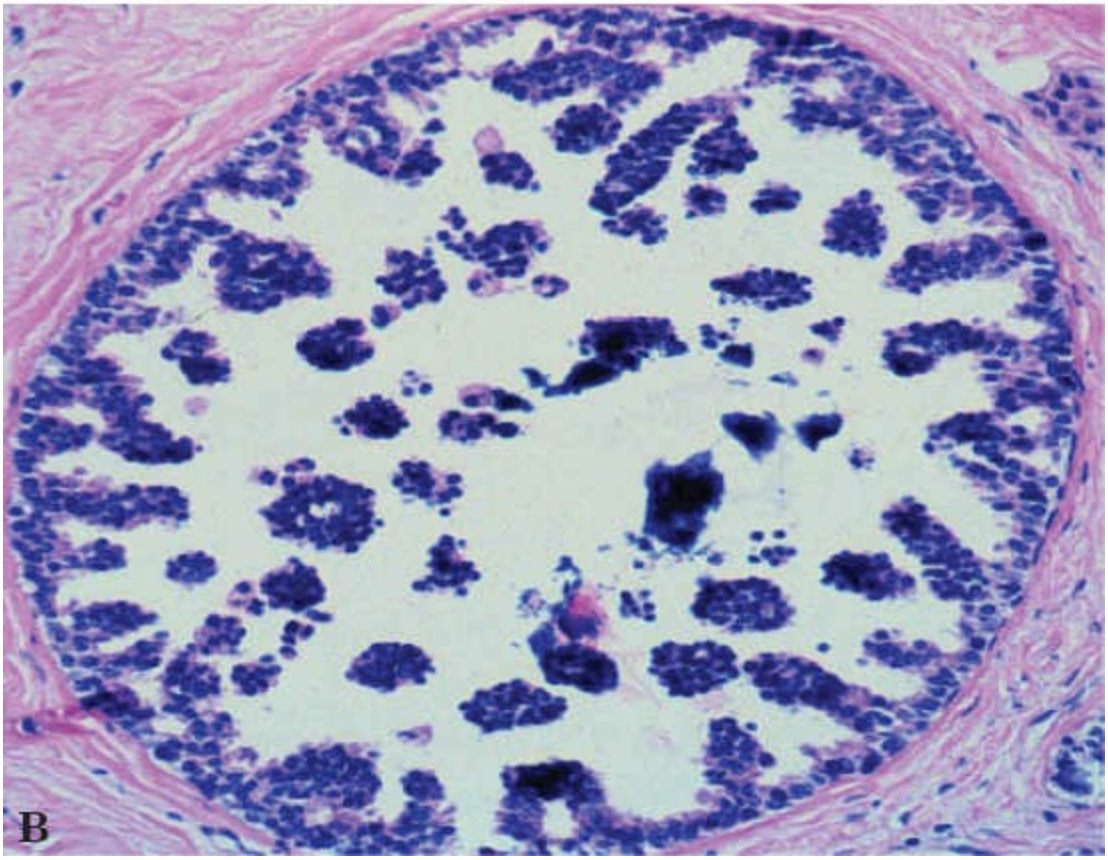
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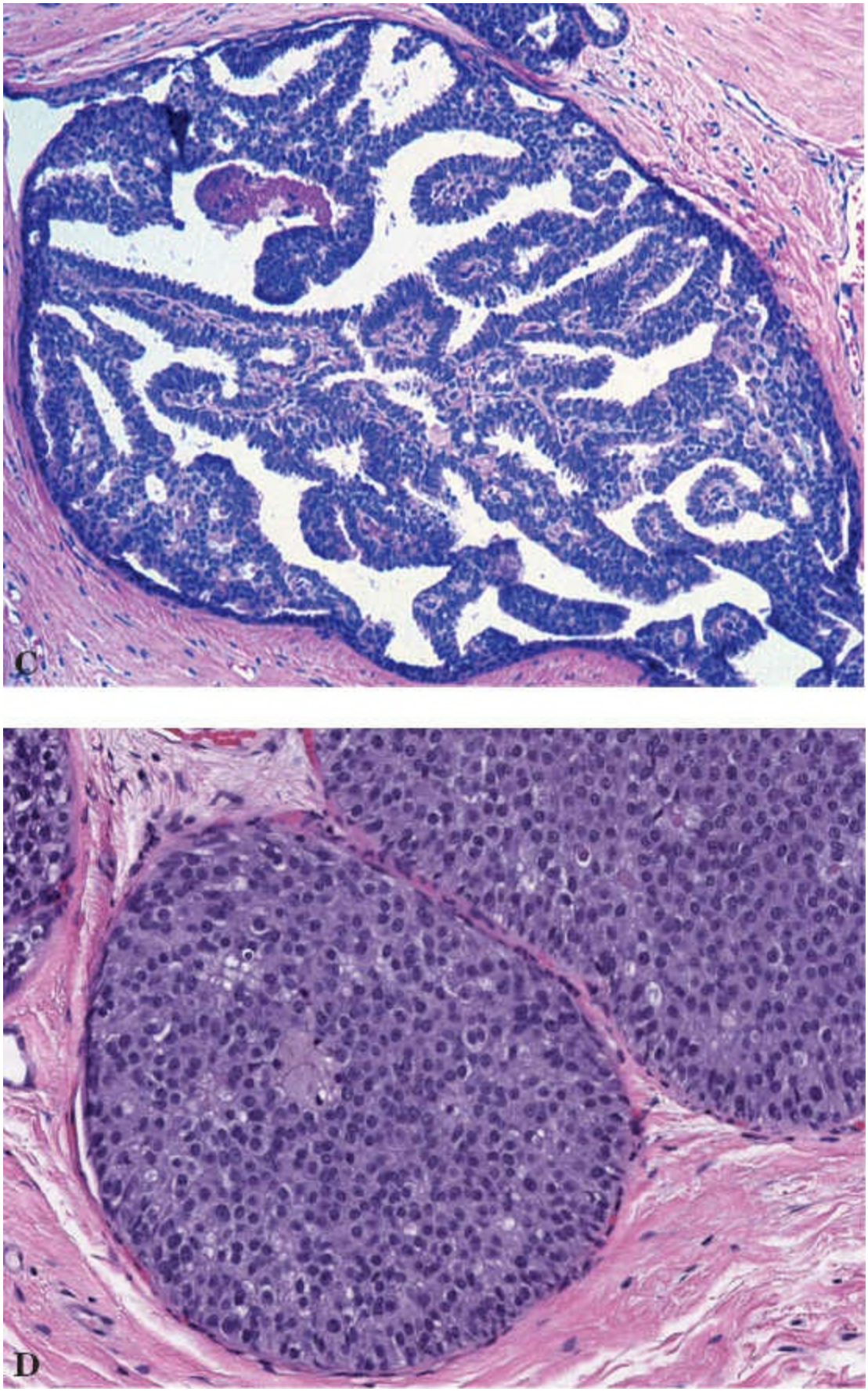


Figure 1.1 Ductal carcinoma in situ (DCIS). Architectural

heterogeneity is a common feature of DCIS. Even in the same lesion, DCIS may show different growth patterns. The most common patterns include cribriform (**A**), micropapillary (**B**), papillary (**C**), and solid (**D**).

Classification of DCIS

DCIS is generally classified as one of five subtypes—comedo, solid, cribriform, micropapillary, and papillary—based on differences in the architectural pattern of the cancer cells and nuclear features. Cribriform, comedo, and micropapillary are the most common subtypes, although two or more patterns coexist in up to 50% of cases.

The classification of noninvasive breast cancer stratifies lesions based on their likelihood of recurrence and incorporates prognostic factors. Lagios et al. (1989) identified high nuclear grade and comedonecrosis as factors predictive of local recurrence. Patients whose tumors had a high nuclear grade and comedonecrosis had a 19% local recurrence rate after lumpectomy alone at an average interval of 26 months, compared with 5% for those patients whose tumors did not have necrosis and were a lower nuclear grade. Subsequently, Silverstein et al. (1995) developed the Van Nuys algorithm to stratify patients into three risk groups using three established predictors of local recurrence: tumor size, margin width, and pathologic classification (i.e., the presence or absence of comedonecrosis and/or high tumor grade). Now updated to include age, the University of Southern California/Van Nuys Prognostic Index Scoring System can be used to determine which patients with DCIS are at greatest risk for recurrence and would therefore benefit from particular forms of locoregional therapy. With the goal being a local recurrence rate of less than 20% at 12 years, surgical excision alone is recommended for scores 4 to 6 and for patients with a score of 7 but have margins ≥3 mm. Excision plus radiation therapy is recommended for patients with a score of 7 and margins <3 mm, a score of 8 and margins ≥3 mm, or a score of 9 and margins ≥5 mm. Mastectomy is recommended for a score of 8 and margins <3 mm; a score of 9 and margins <5 mm; and for all patients with a score of 10 to 12. The USC/VNPI score may be a useful adjunct in therapeutic decision making, but multiple attempts at independently validating the utility of this risk stratification scheme have not been consistent. Currently, there is no universally accepted classification system for DCIS.

Multifocality

Multifocal DCIS is generally defined as DCIS present as two or more foci separated by at least 5 mm within the same breast quadrant. Most investigators believe that multifocal disease in fact represents intraductal spread from a single focus of DCIS. By careful serial subsectioning, Holland et al. (1990) demonstrated that multifocal lesions that appeared to be separate using traditional pathologic techniques actually originated from the same focus in 81 of 82 mastectomy specimens.

Multicentricity

Multicentric DCIS is defined as DCIS presenting as separate, discontinuous foci of disease involving more than one quadrant. The reported incidence of multicentricity may depend on the extent of the pathologic review and therefore varies from 18% to 60%. Because mammary lobules are not constrained by artificially imposed quadrant segregations, cursory pathologic examination may incorrectly interpret contiguous intraductal spread as multicentricity. Approximately 96% of all local recurrences after treatment of DCIS occur in the same quadrant as the index lesion, implicating residual untreated disease rather than multicentricity as the cause of recurrence.

Microinvasion

The eighth edition of the American Joint Committee on Cancer (AJCC) staging system defines microinvasion as invasion of breast cancer cells through the basement membrane at one or more foci, none of which exceeds a dimension of 1 mm. DCIS is a T0 lesion and is classified as stage 0 cancer; DCIS with microinvasion is considered T1mi, and upstages DCIS from stage 0 to stage I disease, i.e., the earliest stage of invasive cancer, in the AJCC staging system. By definition, DCIS does not have the ability to metastasize to axillary lymph nodes or distant sites, whereas DCIS with microinvasion does. Axillary metastasis has been reported in 0% to 20% of patients with DCIS with microinvasion.

The incidence of microinvasion in DCIS varies according to the size and extent of the index lesion. Lagios et al. (1989) reported a 2% incidence of microinvasion in patients with DCIS measuring less than 25 mm in diameter, compared with a 29% incidence of microinvasion in those with lesions larger than 26 mm. The incidence of microinvasion is also higher in patients with high-grade or comedo-type DCIS with necrosis and in

patients with DCIS who present with a palpable mass or nipple discharge.

Historically, patients with DCIS with microinvasion have been observed to have a worse prognosis compared with those who have DCIS alone. Mirza et al. (2000) reported the long-term results of breast-conserving therapy in patients with DCIS, DCIS with microinvasion, and T1 invasive breast cancers. The 20-year disease-specific survival rates in patients with DCIS were better than those among patients with DCIS with microinvasion or with T1 invasive tumors. Patients with microinvasion and those with T1 tumors had similar survival rates. In a retrospective study of 1,248 serially sectioned DCIS tumors, de Mascarel et al. (2002) reported a 10.1% incidence of axillary metastases in cases of DCIS with microinvasion. Patients with DCIS had a better 10-year distant metastasis-free survival rate than patients with DCIS with microinvasion (98% and 91%, respectively). The overall survival rate was also better in patients with DCIS (96.5% vs. 88.4%). However, the metastasis-free and overall survival rates were worse in patients with invasive ductal carcinoma compared with those with DCIS with microinvasion. These results suggest that DCIS with microinvasion should be characterized as a small invasive tumor with a good outcome and that the therapeutic approach for these patients should be similar to that for patients with invasive cancer.

However, more recent studies have pointed toward DCIS with microinvasion having a more similar natural history to pure DCIS than to early-stage invasive disease. In a review of 393 patients treated at Yale between 1973 and 2004, there was no statistically significant difference between patients with DCIS and those with DCIS with microinvasion with regard to the presence of axillary metastases (in those who had axillary staging) or the likelihood of recurrence (locoregional and distant) or overall survival (Parikh et al., 2012).

Diagnosis

Clinical Presentation

Before the implementation of routine screening mammography, most patients with DCIS presented with a palpable mass, nipple thickening or discharge, or Paget disease of the nipple. Occasionally, DCIS was an incidental finding in an otherwise benign breast biopsy specimen. In patients with palpable lesions, up to 25% demonstrated foci of invasive disease. Now that screening mammography is more prevalent, most cases of DCIS are diagnosed when the tumor is still clinically occult. Patients

with abnormalities detected by screening mammography should always undergo diagnostic imaging of the contralateral breast because 0.5% to 3.0% of patients have synchronous occult abnormalities or cancers in the contralateral breast. Mammographic images should be compared with previous images, if available, to establish interval changes.

Mammographic Features

On a mammogram, DCIS can present as microcalcifications, a soft-tissue density, or both (Fig. 1.2). Microcalcifications are the most common (80% to 90%) mammographic manifestation of DCIS which, in turn, accounts for 80% of all breast carcinomas presenting with calcifications. Any interval change from a previous mammogram is associated with malignancy in 15% to 20% of cases and most often indicates in situ disease. Holland et al. (1990) described two different classes of microcalcifications: (a) linear branching-type microcalcifications, which are more often associated with high–nuclear-grade, comedo-type lesions; and (b) fine, granular calcifications, which are primarily associated with micropapillary or cribriform lesions of lower nuclear grade and that do not show necrosis. Although the morphology of microcalcifications suggests the architectural type of DCIS, it is not always reliable. Holland et al. also demonstrated that the mammographic findings significantly underestimated the pathologic extent of disease, particularly in cases of micropapillary DCIS. Lesions were more than 2 cm larger by histologic examination than by mammographic estimation in 44% of cases of micropapillary lesions, compared with only 12% of cases of the pure comedo subtype. However, when magnification views were used in diagnostic mammographic examination, the extent of disease was underestimated in only 14% of cases of micropapillary tumors. Hence, magnification views increase the image resolution and are better able to delineate the shape, number, and extent of microcalcifications when compared with mammography alone and should be used routinely in the evaluation of suspicious mammographic findings.

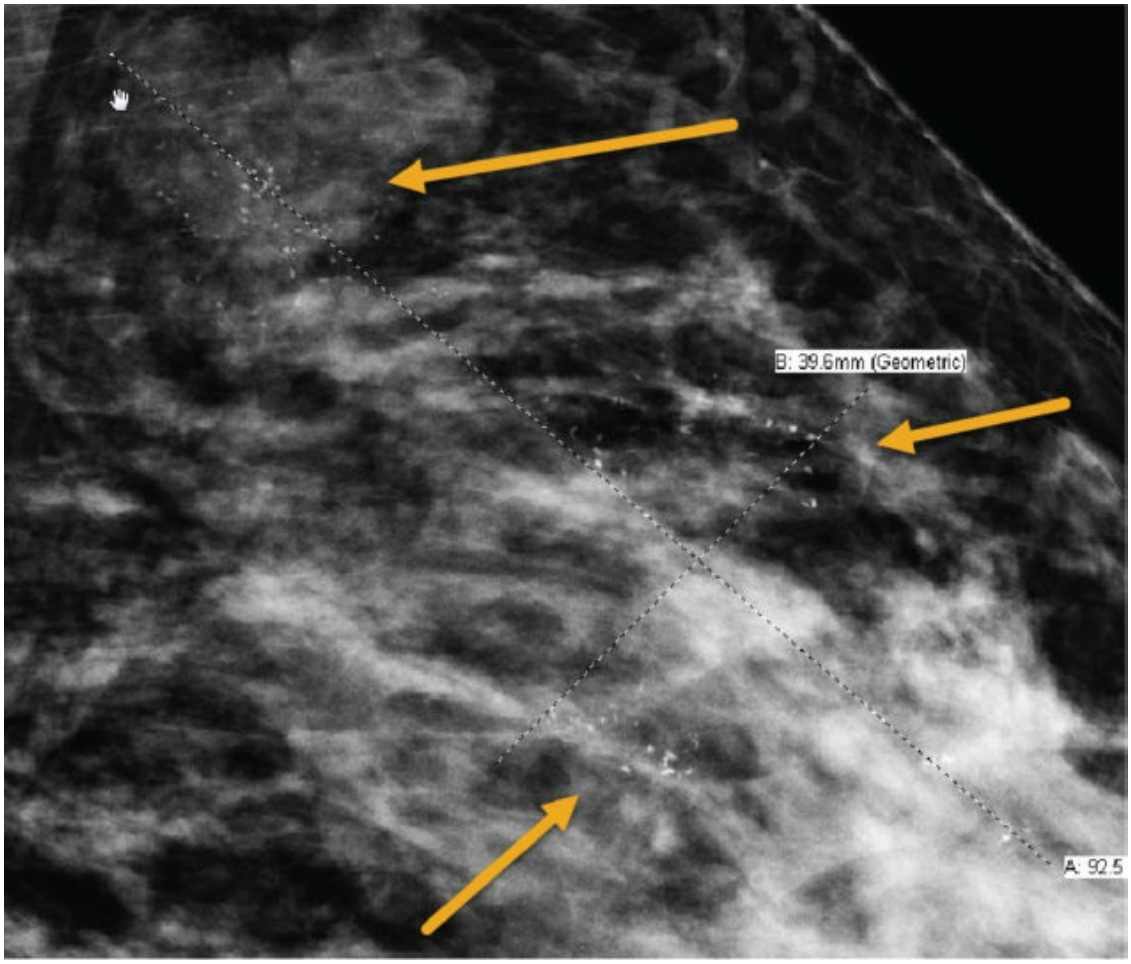


Figure 1.2 Calcifications seen on diagnostic mammography associated with ductal carcinoma in situ (DCIS). Magnification view is shown to demonstrate calcifications spanning approximately 9 cm.

Magnetic Resonance Imaging

Mammography remains the standard for radiographic evaluation of DCIS. The cost and accessibility of magnetic resonance imaging (MRI) make it less feasible as an effective screening method. However, there is evidence that patients at high risk for breast cancer or those with very dense breasts may benefit from screening with MRI. Contrast-enhanced MRI is more sensitive than mammography in the detection of both DCIS and invasive cancer. However, fibrocystic changes and other benign findings can mimic DCIS on MRI, leading to unnecessary biopsies. MRI is increasingly being utilized after initial diagnosis in the preoperative evaluation to identify multicentric and contralateral lesions because presence of either of these may change the surgical treatment strategy. Hollingsworth et al. (2008) reported that MRI detected multicentric disease, defined as a separate focus of cancer more than 5 cm away from the index lesion or

discontinuous growth to another breast quadrant, in 4.3% of 149 patients who presented with DCIS. Lehman et al. (2007) reported the utility of MRI in detecting contralateral breast cancer in a group of 969 patients with unilateral breast cancer, 196 of whom had DCIS. Of the patients with DCIS, MRI prompted additional biopsies in 18 patients. Contralateral breast cancer was detected in five patients (28% of those biopsied and 2.6% of those with DCIS). The sensitivity of detecting contralateral breast cancer was 71%; the specificity was 90%. While MRI is associated with increased likelihood of change in the surgical plan for a patient with unilateral breast cancer, it is unclear whether these altered (and usually more extensive) surgical plans are actually treating clinically significant disease that might have otherwise decreased the patient's disease-free or overall survival. In a review of over 2,300 patients with breast-conserving therapy (BCT, i.e., lumpectomy and radiation) for DCIS at Memorial Sloan Kettering between 1997 and 2010, there was no association between receipt of preoperative MRI and risk of locoregional recurrence or contralateral breast cancer, regardless of whether the patient received radiation (Pilewskie et al., 2014).

Diagnostic Biopsy

Stereotactic core-needle or vacuum-assisted biopsy is the preferred method for diagnosing DCIS. Calcifications that appear faint on mammogram or that are deep in the breast and close to the chest wall may be difficult to target with stereotactic biopsy. In addition, use of stereotactic biopsy in patients above the weight limit of the stereotactic system (about 150 kg) and in patients with very small breasts, may be impossible. Patients who cannot remain prone or who cannot cooperate for the duration of the procedure are also not good candidates for stereotactic biopsy. Bleeding disorders and the concomitant use of anticoagulants are relative contraindications. Biopsy specimens should be radiographed to document the sampling of suspicious microcalcifications. Care should be taken to mark the biopsy site with a metallic clip in the event that all microcalcifications are removed with the biopsy procedure. In the final biopsy procedure report, it is important to report the needle gauge used, how many cores were obtained, and an estimate as to what percentage of the calcifications was removed.

Because stereotactic core-needle and vacuum-assisted biopsy specimens represent only a sample of an abnormality observed on mammography, the

results are subject to sampling error. Invasive carcinoma is found on excisional biopsy in 20% of patients in whom DCIS was diagnosed by a stereotactic core-needle biopsy. Thus, if the core-needle biopsy results are discordant with the findings of imaging studies, a wire- or seed-localized excisional biopsy can be performed to establish the diagnosis. After diagnosis using stereotactic core-needle biopsy, approximately 20% to 30% of patients with ADH, up to 20% of patients with radial scar, and approximately 5% to 10% of patients with flat epithelial atypia (FEA) are found to have a coexistent carcinoma near the site of the biopsy when complete excision is performed. Therefore, when the final pathologic studies from core-needle biopsy procedures indicate either of these diagnoses, consideration should be made for excisional biopsy, though in the case of pure FEA, there is some evidence to suggest that surgical excision is not necessary if all calcifications are removed at the time of biopsy (Calhoun et al., 2015). Patients who are not candidates for stereotactic biopsy or who have stereotactic biopsy results that are inconclusive or discordant with the mammographic findings should undergo excisional biopsy. This technique is performed with the assistance of preoperative wire or seed localization of the mammographic abnormality in conjunction with the previously placed metallic clip marking the biopsy site. Postexcision specimen radiography is essential to confirm the removal of microcalcifications or targeted lesion. The excisional biopsy should be performed with the aim of obtaining a margin-negative resection that can serve as the definitive surgery.

Treatment

The diagnosis of DCIS is followed by surgical treatment with breast-conserving surgery (also referred to as segmental mastectomy, partial mastectomy, lumpectomy, or wide local excision) or mastectomy. Most patients who undergo breast-conserving surgery receive postoperative radiation therapy to improve local control. Postoperative endocrine therapy with tamoxifen or an aromatase inhibitor should also be considered for those patients whose tumors are hormone (estrogen and/or progesterone) receptor positive.

Mastectomy Versus Breast-conserving Therapy

Historically, DCIS was treated with mastectomy. The rationale for performing total mastectomy in patients with DCIS was based on the high

incidence of multifocality and multicentricity, as well as on the risk of occult invasion associated with the disease. Thus, mastectomy remains the standard with which other proposed therapeutic modalities are compared. However, in patients with DCIS, there are no prospective trials comparing outcomes after mastectomy with those after breast-conserving surgery. A retrospective review by Balch et al. (1993) documented a local relapse rate of 3.1% and a mortality rate of 2.3% after mastectomy for DCIS. The cancer-related mortality rate following mastectomy for DCIS was 1.7% in a series reported by Fowble (1989) and ranged from 0% to 8% in a review by Vezeridis and Bland (1994).

In one of the largest studies comparing breast-conserving therapy with mastectomy, Silverstein et al. (1992) examined 227 cases of DCIS without microinvasion. In this nonrandomized study, patients with tumors smaller than 4 cm with microscopically clear margins underwent breast-conserving surgery and radiation therapy, whereas patients with tumors larger than 4 cm or with positive margins underwent mastectomy. The rate of disease-free survival at 7 years was 98% in the mastectomy group compared with 84% in the breast-conserving surgery group ($P = 0.038$), with no difference in overall survival rates. In a meta-analysis, Boyages et al. (1999) reported a recurrence rate of 22.5%, 8.9%, and 1.4% following breast-conserving surgery alone, breast-conserving surgery with radiation therapy, and mastectomy, respectively. In patients who underwent breast-conserving surgery alone, approximately 50% of the recurrences were invasive cancers. Although recurrence rates are higher in patients who undergo breast-conserving surgery than in patients who undergo mastectomy, no survival advantage has been shown for patients treated with mastectomy.

Technique of Breast-conserving Surgery

The goal of breast-conserving surgery is to remove all suspicious calcifications and obtain negative surgical margins. Because DCIS is usually nonpalpable, breast-conserving surgery can be performed with mammographically or sonographically guided placement of a localizing wire or radioactive seed. Seed localization of nonpalpable breast lesions is increasingly used in US and—through multidisciplinary collaboration with surgeons, radiologists, and pathologists—has the advantage of allowing a less obtrusive marker to be placed at a time that is uncoupled from the time of surgery. At most centers where seed localization is performed, an I-125

radioactive seed is placed by a radiologist within the area of disease in much the same way wire localization has historically been performed. The seed is localized intraoperatively using a gamma probe placed on the appropriate setting to detect radioactive decay for the seed's isotope label, and the surrounding tissue is excised. Resection of the seed, lesion, and previously placed clip are confirmed intraoperatively by pathologic and radiologic review. Nonradioactive methods of seed localization including ultrasound and magnetic seeds are also available.

Intraoperative orientation of the specimen with two or more marking sutures is critical for margin analysis. In addition, specimen radiography is essential to confirm the removal of all microcalcifications. In patients with extensive calcifications, bracketing of the calcifications with two or more seeds or wires may assist in the excision of all suspicious calcifications.

After whole-specimen radiography, the specimen should be inked and then serially sectioned for pathologic examination to evaluate the margin status and extent of disease. Chagpar et al. (2003) demonstrated that intraoperative margin assessment with the use of sectioned-specimen radiography enabled reexcisions to be performed at the same surgery if the microcalcifications extended to the cut edge of the specimen, minimizing the need for second procedures for margin control. After margins are deemed adequate intraoperatively, the boundary of the resection cavity is marked with radiopaque clips to aid in the planning of postoperative radiation therapy and to facilitate mammographic follow-up.

The goal of breast-conserving surgery is to obtain tumor-free margins. A detailed pathologic study of DCIS, reported by Holland et al. (1990), demonstrated that up to 44% of lesions extended more than 2 cm further on histologic examination than that estimated by mammography. However, in most women, a 1- to 2-cm margin around the lesion is not feasible since the cosmetic result would be poor. The 2016 guidelines of the National Comprehensive Cancer Network (NCCN) dictate that close (<1 mm) margins are inadequate for DCIS and should be reexcised, but for patients in whom the border of disease is the fibroglandular boundary (i.e., chest wall) or skin, radiation with a boost to the surgical scar is an acceptable alternative to reexcision. In 2015 a multidisciplinary panel was convened by the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology to review a meta-analysis and other literature concerning margin width and ipsilateral breast tumor recurrence (IBTR) in patients with DCIS

undergoing breast-conserving therapy (Morrow, 2016). The meta-analysis included 20 studies with 7,883 patients and 865 IBTRs with a median follow-up of 78.3 months. The panel reported that positive margins were associated with a twofold increased risk of IBTR compared with patients who had negative margins. They also reported that margins of at least 2 mm were associated with a lower risk of IBTR compared with narrower margins. Patients treated with wide local excision alone without radiation therapy had substantially higher rates of IBTR compared with patients undergoing wide local excision and whole breast irradiation regardless of the margin width. Rates of IBTR and contralateral breast cancer were reduced in patients who received tamoxifen, however, there was no significant impact on IBTR in patients with negative margins when compared with patients receiving placebo. The panel concluded that a 2-mm margin was adequate in patients undergoing breast-conserving surgery and whole breast irradiation for DCIS. Clinical judgment should be utilized in deciding on the need for reexcision in patients with margins <2 mm.

Radiation Therapy

Most patients with DCIS who undergo breast-conserving surgery should receive postoperative radiation therapy. Five prospective randomized studies have evaluated the role of radiation therapy following breast-conserving surgery for DCIS. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial (Fisher, 1993), 818 women with localized DCIS enrolled from 1985 to 1990 and were randomized to breast-conserving surgery or breast-conserving surgery plus radiation therapy after margin-negative resections. At a follow-up time of 12 years, radiation therapy was associated with a reduction in the cumulative incidence of noninvasive ipsilateral breast tumors from 14.6% to 8% and with a reduction in the incidence of invasive ipsilateral breast tumors from 16.8% to 7.7%. After 15 years, radiation therapy was associated with a reduction in the cumulative incidence of noninvasive ipsilateral breast tumors from 15.7% to 8.8% (hazard ratio [HR] = 0.53, 95% confidence interval [CI] 0.35–0.80, $p < 0.001$) and a reduction in the incidence of invasive ipsilateral breast tumors from 19.4% to 8.9% (HR 0.48, CI 0.33–0.69, $p < 0.001$). There was no difference in the 15-year overall survival rate in the two groups (Wapnir, 2011).

The overall benefit of radiation therapy for patients with DCIS was also

observed in the European Organization for Research and Treatment of Cancer (EORTC) 10853 trial (Julien, 2000). In this trial, 1,010 women with DCIS treated between 1986 and 1996 were randomized to breast-conserving surgery or breast-conserving surgery plus radiation therapy. Initially, at a median follow-up time of 4.25 years, radiation therapy was associated with a reduction in the incidence of noninvasive ipsilateral breast tumors from 8.8% to 5.8% and with a reduction in the incidence of invasive ipsilateral breast tumors from 8.0% to 4.8%. The lower recurrence rates in this trial when compared with those in the NSABP B-17 were attributed to the shorter follow-up time. However, at 15 years, radiation therapy was associated with a reduction in noninvasive recurrence from 16% to 8% (HR 0.49, CI 0.33–0.73, $p = 0.003$) and in invasive recurrence from 16% to 10% (HR 0.61, CI 0.42–0.87, $p = 0.007$), demonstrating rates of recurrence and magnitudes of risk reduction that are similar to those observed in long-term follow-up of patients in the NSABP B-17 trial. Likewise, there was no difference in the 15-year overall survival rate in the two groups (Donker, 2013).

A third trial, conducted by the United Kingdom (UK) Coordinating Committee on Cancer Research, enrolled 1,701 women from UK, Australia, and New Zealand, between 1990 and 1998. This trial confirmed the benefits of radiation therapy for local control (Houghton, 2003). After margin-negative lumpectomy, patients were randomized to one of three arms: (1) no adjuvant treatment, (2) adjuvant radiation therapy or tamoxifen, or (3) adjuvant radiation therapy plus tamoxifen. After a median follow-up time of 4.4 years, there was a reduction in the incidence of noninvasive ipsilateral breast tumors from 7% to 3% (HR 0.36, CI 0.19–0.66, $p = 0.0004$) and a reduction in the incidence of invasive ipsilateral tumors from 6% to 3% (HR 0.45, 0.24-0.85, $p = 0.01$) when those who received radiation were compared to those who did not. After a median follow-up of 12.7 years, radiation continued to be associated with a reduced incidence of both ipsilateral DCIS (HR 0.38, CI 0.22–0.63, $p < 0.0001$) and ipsilateral invasive disease (HR 0.32, CI 0.19–0.56, $p < 0.0001$; Cuzick, 2011).

The Radiation Therapy Oncology Group (RTOG) 9804 trial was a US/Canadian trial that randomized patients with low- or intermediate-grade DCIS less than 25 mm and excised with margins of at least 3 mm to postoperative radiation therapy or observation with the option of tamoxifen use in each group. The trial was closed early due to poor

accrual, with only 636 patients enrolled between 1998 and 2006 instead of the 1,790 participants that had been planned. At 7 years, there were 2 (0.9%) ipsilateral local failures in the cohort that received radiation and 19 local failures (6.7%) in the observation only group (HR 0.11, CI 0.03–0.47, $p < 0.001$) but increased rate of grade 1 and 2 acute toxicities (i.e., toxicities that occurred within 90 days of the start of treatment and scored using the National Cancer Institute Common Toxicity Criteria) among patients who received radiation (76% vs. 30%, $p < 0.001$, McCormick, 2015). The lower than expected recruitment may explain why the rates of local failure and the concomitant reductions in risk are significantly lower than those observed in other trials.

Finally, in the SweDCIS trial, 1,046 women diagnosed with DCIS between 1987 and 1999 were randomized to either be observed or to receive adjuvant radiation therapy after lumpectomy. At 20-year follow-up, radiation therapy reduced the risk of local recurrence by 37.5%, though breast cancer–specific death and overall survival were the same between the irradiated and observed cohorts (Wärnberg, 2014).

Taken together, these five prospective randomized trials demonstrate that the addition of radiation therapy following breast-conserving therapy for DCIS results in an approximately 50% relative reduction in breast cancer recurrence.

Whole-breast irradiation (WBI) has been the standard for patients undergoing breast-conserving surgery and is generally well tolerated. The most common morbidity is radiation-induced skin changes including discoloration, fibrosis, and telangiectasias. Rare, severe side effects include damage to the heart and lungs, and development of angiosarcoma, a radiation-induced secondary malignancy.

Partial Breast Irradiation

In patients not receiving radiation therapy, local recurrences in the breast tend to occur in the immediate vicinity of the surgical resection cavity. Hence, the main effect of whole-breast irradiation is likely the reduction of local recurrence in the immediate area surrounding the original tumor bed. On the basis of this knowledge, some have suggested that equivalent local control can be achieved by using partial breast irradiation, which focuses the treatment on the tissue surrounding the surgical resection cavity. Accelerated partial breast irradiation is a technique where high-dose radiation is delivered over a shorter period of time to a limited region of

the breast surrounding the primary tumor site. The treatment is completed over 4 to 5 days, whereas conventional whole-breast external beam radiation therapy typically requires 4 to 6 weeks. Several methods of partial breast irradiation have been described, including brachytherapy via multiple catheters placed in the breast parenchyma, localized conformal three-dimensional external beam radiation therapy (3D-XRT), brachytherapy via bead or seed implants, single-dose intraoperative radiation therapy, and brachytherapy via a balloon catheter inserted into the cavity after breast-conserving surgery.

In 2010, Jeruss et al. presented an update on the American Society of Breast Surgeons (ASBS) Accelerated Partial Breast Irradiation (APBI) Registry Trial. Of 194 enrolled patients with DCIS, 63 had at least 5 years of follow up. Of these, 92% had favorable cosmetic results. The 5-year locoregional recurrence rate of 3.39% compared favorably with the rate of 7.5% reported using whole-breast radiation in the NSABP B-17 trial. The NSABP B-39/RTOG 0413 trial, which opened in 2005, is a randomized phase III trial developed to determine whether patients who received APBI via 3D-XRT, brachytherapy, or single-entry intracavitary delivery had rates of local control comparable to those of patients who received conventional WBI. This trial will provide additional information about the potential role for APBI in patients with DCIS and those with invasive breast cancer as well. Enrollment was limited to women with no more than 3 cm of DCIS or invasive stage I or II breast cancer and limited nodal disease (≤3 lymph nodes) who underwent margin-negative lumpectomy with systemic hormonal therapy and chemotherapy administered at the discretion of their treating physician. The primary endpoint was local tumor control, and the secondary endpoints were disease free and overall survival, cosmetic results, and treatment toxicity. In 2013, Olivotto and colleagues published the results of a planned interim analysis, which demonstrated increased rates of adverse cosmesis and late radiation toxicity with APBI administered via 3D-XRT as compared to WBI. The trial closed for accrual on April 16, 2013, and final data collection for the primary outcome measure is expected to be complete in 2018.

Omitting Radiation Therapy

A recent survey (Jagsi, 2010) demonstrated that 95% of women with breast cancer and strong indications for post-lumpectomy radiation went on to receive it, but rates of post-lumpectomy radiation therapy use have

been shown to vary, depending on the region of the country that the patient lives in, the age of the patient, and the disease being treated. Among patients who undergo BCT for DCIS, only 50% are estimated to receive adjuvant radiation.

Many patients choose mastectomy over breast-conserving surgery for DCIS because they are not able or willing to complete 6 weeks of daily radiation therapy secondary to social or health considerations. Other patients who are candidates for breast-conserving surgery choose to undergo a mastectomy because of concerns about postradiation complications. Breast-conserving surgery alone (i.e., without radiation therapy) may be sufficient in a select subgroup of patients with DCIS. Initial data that supported the use of breast-conserving surgery alone in the treatment of DCIS came from a study by Lagios et al. (1989) in which 79 patients with mammographically detected DCIS underwent margin-negative excision alone. After a follow-up time of 124 months, the local recurrence rate was 16% overall, specifically, 33% for the subgroup of patients with high-grade lesions and comedo necrosis versus only 2% for the patients with low- or intermediate-grade lesions.

As discussed earlier, the USC/VNPI score can be a helpful tool in clinical decision making. But even though margin width is an independent prognostic factor for recurrence using the USC/VNPI score, it is unlikely that margin width alone can identify the patients with DCIS treated with breast conservation for whom radiation therapy can be safely omitted. In a retrospective analysis of 469 patients with DCIS who underwent breast conservation with margins that were at least 10 mm, Silverstein et al. (1999) did not detect a lower recurrence rate when postoperative radiation therapy was employed. In contrast, even on reanalysis of the NSABP B-17 data, all patient cohorts benefited from radiation therapy, regardless of the clinical or mammographic tumor characteristics. Furthermore, Wong et al. (2003, 2014) reported the early termination of a prospective single-arm trial conducted at the Dana-Farber/Harvard Cancer Center in which radiation therapy was omitted in patients with grade 1 to 2 DCIS that was no more than 25 mm and excised with 10 mm or greater margins. At a median follow-up of 3.3 years, the number of local recurrences observed was 2.5% per patient-year, corresponding to a 5-year rate of 12.5%.

In 2010, Rudloff and colleagues at Memorial Sloan Kettering published a multivariable nomogram to estimate risk for local recurrence in women with DCIS treated with breast-conserving surgery. The nomogram

incorporates commonly available factors that have previously been shown to affect risk of ipsilateral breast tumor recurrence. These include age at diagnosis, family history, type of patient presentation (radiologic or clinical), nuclear grade, necrosis, margins, number of excisions, and receipt of radiation and/or adjuvant endocrine therapy. The nomogram calculates an actual, individualized estimate of absolute risk of ipsilateral breast tumor recurrence at 5 or 10 years, which can be weighed against the use of available adjuvant treatment options.

In addition to the five clinical trials discussed earlier, there are two large, prospective, observational studies designed to investigate the role of observation versus radiation therapy after breast-conserving therapy in patients with DCIS. As mentioned earlier, Wong and colleagues at Harvard conducted a single-arm, phase III observational study examining long-term outcomes in women with small (≤2.5 cm), low- and intermediate-grade DCIS who were treated with lumpectomy and margins ≥1 cm and did not receive adjuvant tamoxifen or radiation. With a median follow-up of 11 years, 13% (19 of 143) of patients experienced local recurrence, approximately two-third of which were DCIS. In the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN; formerly known as the Eastern Cooperative Oncology Group) Cancer Research Group E5194 study, patients with low- or intermediate-grade DCIS smaller than 25 mm (cohort 1), or high-grade DCIS smaller than 10 mm (cohort 2), with excisional margins of at least 3 mm, underwent breast-conserving surgery without radiation therapy; 30% of patients received tamoxifen. At 12 years, 14.4% of the participants in cohort 1 experienced an in-breast event, while 24.6% of those in cohort 2 experienced an in-breast event ($p = 0.0003$), and this difference was driven by a statistically significant difference ($p = 0.02$) in noninvasive recurrence. In addition, membership in cohort 2 and larger tumor size were both found to be associated with increased likelihood of recurrence (Solin, 2015).

Finally, in patients over 70, there is increasing evidence that radiation therapy—depending on the aggressiveness of the DCIS and the expected life expectancy of the patient—can be omitted on a case-by-case basis.

Endocrine Therapy

Two prospective randomized trials have evaluated the effect of tamoxifen on outcome in patients with DCIS treated with breast-conserving therapy.

In the NSABP B-24 trial (Fisher, 1999), 1,804 women with DCIS were randomly assigned to breast-conserving surgery and radiation therapy followed by either tamoxifen at 20 mg/day or a placebo for 5 years. Sixteen percent of the women in this study had positive resection margins. At 7 years of follow-up, women who received tamoxifen had fewer breast cancer events than did the placebo group (10.0% vs. 16.9%). Among those who received tamoxifen, the rate of ipsilateral invasive breast cancer was 2.6% at 7 years compared with 5.3% in the control group. Tamoxifen also decreased the 7-year cumulative incidence of contralateral breast neoplasms (invasive and noninvasive) to 2.3% compared with 4.9% in the control group. The benefit of tamoxifen therapy also extended to patients with positive margins or margins of unknown status. There was no difference in the 7-year overall survival rate, which was 95% in both the tamoxifen and the placebo groups. Most deaths occurred before recurrence developed and were not necessarily related to breast cancer. A subgroup analysis based on retrospectively determined estrogen receptor (ER) status (Allred, 2012), indicated that women with ER-positive (ER+) DCIS who received tamoxifen had over a 50% reduction in their relative risk of subsequent breast cancer at 10 years when compared with those who received placebo. Among patients with ER-negative (ER-) DCIS, there was no added benefit from tamoxifen.

In the United Kingdom Coordinating Committee on Cancer Research trial (discussed above), radiation therapy had the greatest impact on reducing ipsilateral breast cancer events after approximately 4 years of follow-up, whereas tamoxifen added to radiation therapy did not result in significant additional benefit. But the relatively short follow-up time and complex design of this trial made direct comparison of the initial results to those of the NSABP B-24 trial difficult. In a subsequent analysis of the UK trial for which median follow-up was 12.7 years (Cuzick, 2011), tamoxifen was found to have reduced the incidence of all new breast events (HR 0.71, CI 0.58–0.88; $p = 0.002$), a finding that was entirely driven by a statistically significant reduction in both recurrent ipsilateral DCIS (HR 0.70, CI 0.51–0.86; $p = 0.03$) and contralateral invasive and noninvasive tumors (HR 0.44, CI 0.25–0.77, $p = 0.005$) as there was no effect on ipsilateral invasive disease (0.95, CI 0.66–1.38; $p = 0.8$).

Tamoxifen should be reserved for patients with ER+ tumors. The use of tamoxifen has been associated with vasomotor symptoms, deep vein thrombosis, pulmonary embolism, and increased cataract formation. The

risk of endometrial cancer is increased two to seven times among patients who receive the drug. Tamoxifen is also associated with increased rates of stroke and benign ovarian cysts. Accordingly, although tamoxifen plays an important role in the adjuvant treatment of DCIS, better tolerated alternatives have been the subject of significant investigation.

Aromatase inhibitors have been shown to be beneficial in the adjuvant treatment of invasive breast cancer in postmenopausal women with ER+ disease. These agents have fewer cardiovascular side effects than tamoxifen and may be beneficial in the adjuvant treatment of patients with DCIS following breast-conserving surgery. Two randomized prospective clinical trials opened in 2003—NSABP B-35 and the International Breast Cancer Intervention Study (IBIS-II)—to compare the adjuvant use of tamoxifen versus the aromatase inhibitor anastrozole (Arimidex) following breast-conserving surgery in patients with a diagnosis of DCIS.

NSABP-35 was a phase III, double-blinded controlled trial that randomized over 3,000 patients from 333 US and Canadian centers treated between 2003 and 2006 to receive either 20 mg of tamoxifen every day or 1 mg anastrozole every day for 5 years (Margolese, 2016). After median follow-up of 9 years, there were 122 interval events (defined as local, regional, or distant recurrence, or contralateral breast cancer, invasive disease, or DCIS) in the tamoxifen cohort and 90 events among those who received anastrozole (HR 0.73, CI 0.56–0.96, $p = 0.0234$), with anastrozole only being superior to tamoxifen in women younger than 60. Rates of venous thromboembolic events were also higher among those who received tamoxifen.

IBIS-II was a phase III, double-blinded randomized controlled trial that enrolled postmenopausal women aged 40 to 70 years old from 18 countries over the course of 9 years, from 2003 to 2012 (Cuzick, 2014). Participants were randomized to receive either daily anastrozole 1 mg or placebo for 5 years. After a median follow-up of 5 years, 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) developed breast cancer (HR 0.47, CI 0.32–0.68, $p < 0.0001$), representing a >50% reduction in risk.

These two trials demonstrate that anastrozole is a reasonable alternative to tamoxifen for adjuvant treatment of ER+ DCIS, additional investigation is warranted to assess the safety and efficacy of other aromatase inhibitors in this setting.

Observation Only

As previously discussed, much of the increased incidence in DCIS is likely due to increased detection of DCIS subtypes of unclear long-term significance. Three ongoing trials have been designed to examine whether some patients with DCIS can be spared any form of locoregional or systemic treatment. LORD (LOw Risk DCIS) is a multicenter, international (Belgium and the Netherlands), noninferiority trial launched by the European Organisation for Research and Treatment of Cancer (EORTC) in January 2017. The trial compares two strategies for management of low-grade DCIS: for the experimental arm, patients only receive active surveillance with annual mammography and do not receive any locoregional or endocrine therapy, while in the comparator arm, patients receive standard surgical treatment—which can consist of lumpectomy only, lumpectomy and radiation, or mastectomy—with or without endocrine therapy. LORIS is a UK-based, noninferiority controlled trial that is open to women with asymptomatic low-grade or intermediate-grade DCIS who will be randomized either to surgery followed by standard adjuvant treatment and postoperative annual mammographic follow-up or to annual mammographic follow-up alone with no surgical treatment, i.e., active monitoring. The primary endpoint is development of ipsilateral invasive breast cancer, and enrollment opened in July 2014. The COMET (Comparison of Operative versus Medical Endocrine Therapy for Low Risk DCIS) trial is based in US and received federal funding in 2016. Participants will be recruited from 100 sites over the course of 4 years and will be randomized to either undergo standard of care (including surgery and radiation) or active surveillance, with participants in both arms free to choose endocrine therapy.

Axillary Node Staging

Because DCIS is a noninvasive disease, lymph node involvement is not expected. Indeed, if a patient presents with DCIS in the breast but is found to have cancer in the lymph nodes preoperatively, the patient has, by definition, invasive breast cancer and not DCIS. In cases where patients have large tumors (>4 cm) or extensive microcalcifications, a focus of invasion can be missed because of limited pathologic sampling (as discussed earlier, a 20% to 30% rate of concomitant invasive cancers has been reported on final pathology in patients who were diagnosed with DCIS on stereotactic biopsy). Such patients, as well as those with high-grade or palpable disease, are at higher risk for lymph node metastasis and

may also warrant sentinel lymph node (SLN) mapping, particularly if they are undergoing mastectomy or if breast-conserving surgery is to be followed by oncoplastic tissue arrangement. The risk of missing disease in the lymph nodes must be weighed against the risk of lymphedema associated with SLN dissection in each patient. In a study by Cox et al. (1998), the combination of hematoxylin–eosin staining and immunohistochemistry revealed that 6% of patients with newly diagnosed DCIS had metastatic disease in the sentinel nodes. Klauber-DeMore et al. (2000) found that SLNs were positive for cancer among 12% of patients with DCIS considered to be at high risk for invasion and among 10% of patients who had DCIS with microinvasion. In a recent study from the MD Anderson Cancer Center, Francis et al. (2015) examined the incidence of positive nodes and the clinical significance of these findings in 1,234 patients with an initial diagnosis of DCIS planned for SLN dissection. There were positive findings in the SLNs in 132 (10.7%) patients. The findings included isolated tumor cells in 66 (5.4%) patients, micrometastases in 36 (2.9%) and macrometastases in 30 (2.4%). There was upstaging in the primary tumor in 327 (26.5%) patients to microinvasion or invasive cancer. Factors predicting a positive SLN were diagnosis by excisional biopsy, papillary histology, DCIS >2 cm, more than three interventions prior to SLN dissection (needle biopsy, excisional biopsy, etc.), microinvasion or invasive cancer. It was noted that with increasing numbers of preoperative interventions (biopsy, needle localization, etc.), there was a higher likelihood of positive SLN findings with the majority being isolated tumor cells (44/907, 4.2%) or micrometastases (12/907, 1.3%). There were no macrometastases identified in the SLNs of patients with pure DCIS. The high incidence of isolated tumor cells in the SLNs with increasing preoperative interventions supports the concept of benign mechanical transport of epithelial cells during manipulation of the primary tumor. At a median follow-up of 61.7 months, there was no difference in disease-free survival outcomes in the patients with pure DCIS with or without positive SLN findings. In general terms, SLN dissection should be limited to patients who undergo mastectomy for large, high-grade DCIS because it is difficult to perform lymphatic mapping (discussed along with sentinel node biopsy in Chapter 2) after a mastectomy if invasive cancer is found in the mastectomy specimen.

Predictors of Local Relapse

Several features of DCIS are associated with a less favorable clinical course. Pathologic variables, such as large tumor size (>3 cm), high nuclear grade, comedo-type necrosis, and positive margins, are associated with a greater risk of local recurrence. Involved margins of resection constitute the most important independent prognostic variable for predicting local relapse. As described earlier, the USC/VNPI combines four significant predictors of local recurrence: tumor size, margin width, pathologic classification, and younger patient age (<50 years). A strong family history of breast cancer is associated with an increased risk of local recurrence; however, these factors are not considered absolute contraindications for breast-conserving therapy. Molecular markers, such as overexpression of HER-2/*neu*, nm23, heat shock protein, and metallothionein; low expression of p21, Waf1, and Bcl2; and DNA aneuploidy have been reported to be associated with high-grade comedo lesions, but their importance as independent prognostic variables in DCIS has not been clarified.

In 2011, Solin et al. presented the results of a study examining the prognostic efficacy of Oncotype DCIS, a 12-gene molecular assay modeled on Oncotype DX, which is a 21-gene assay used to assess the likelihood that a given patient's ER+ invasive breast cancer will recur within 10 years of diagnosis and to what extent said patient might be expected to benefit from receiving adjuvant chemotherapy in addition to anti-estrogen therapy. As with Oncotype DX, Oncotype DCIS stratifies patients into three score-based tiers: low risk (<39); intermediate risk (39 to 54); and high-risk (≥55). Using a new, prespecified algorithm that had been optimized for DCIS gene expression, tissue samples from 650 women in the ECOG-ACRIN E5194 trial (see earlier discussion) were tested, and higher Oncotype DCIS Score™ was found to be associated with increased likelihood of both overall (invasive and noninvasive, HR 2.34, CI 1.15–4.59, $p = 0.02$) and invasive-only (HR 3.73, CI 1.34–9.82, $p = 0.01$) ipsilateral breast events at 10 years. However, since the E5194 cohort was, by design, biased toward low-risk DCIS phenotypes, additional validation was sought. Rakovitch and colleagues (2015) subsequently validated Oncotype DCIS in a cohort of 2,720 women with a more diverse distribution of DCIS clinicopathologic characteristics and who had been treated with lumpectomy +/- radiation therapy. The DCIS score was associated with increased risk of both invasive (HR 1.78, CI

1.03–3.05, p = 0.04) and noninvasive (HR 2.43, CI 1.31–4.42, p = 0.005) local recurrence regardless of ER status, though, notably, 94.7% of participants had ER+ disease. Oncotype DCIS holds promise as a clinical decision-making tool in the management of DCIS, but prospective validation is warranted.

Treatment and Outcome of Local Recurrence

The overall survival rate in patients with DCIS is excellent. In the NSABP B-17 trial, only 27 deaths (3.3%) attributed to breast cancer occurred after a median follow-up time of 12 years. In the NSABP B-24 trial, 0.8% of the patients died as a consequence of their breast cancer after 7 years of follow-up. In both trials, and in other studies, approximately 50% of all local recurrences were invasive cancers, and risk of recurrence is greatest within the first 5 years after treatment. The management of local recurrence depends on the therapy the patient received for the primary cancer. In cases of local recurrence in patients who underwent breast-conserving surgery without radiation therapy, reexcision with negative margins and postoperative radiation therapy is recommended. For patients who have recurrent breast cancer after receiving breast-conserving surgery and radiation therapy, mastectomy is usually the preferred treatment. If the recurrent tumor is invasive, staging of the axillary nodes is performed with lymphatic mapping and SLN dissection.

The prognosis after treatment of local recurrence depends on whether the recurrence is invasive or noninvasive. Silverstein et al. (1998) found that among patients with invasive recurrences, the 8-year disease-specific mortality rate was 14.4%, and the distant disease probability was 27.1%. In a follow-up study, Romero et al. (2004) reported a 10-year disease-specific mortality rate of 15% in patients with invasive recurrence. Although most patients with recurrent disease after DCIS do survive, an invasive recurrence is a serious event. Patients with DCIS should undergo long-term follow-up for both recurrent disease and development of new ipsilateral or contralateral primary tumors.

Surveillance

If a patient’s DCIS is associated with calcifications on preoperative imaging, a mammogram should be considered after lumpectomy and prior to radiation therapy to rule out residual microcalcifications. Guidelines from the American Cancer Society recommend that a mammogram be

obtained 4 to 6 months after the completion of radiation therapy to establish a new baseline. Follow-up of patients after breast-conserving surgery with or without radiation therapy should include annual or biannual physical examination and annual mammography for the first 5 years, with an annual physical examination and mammogram thereafter. The most recent NCCN treatment guidelines recommend a physical examination every 6 months for 5 years and annually thereafter. Whether these measures improve the detection of recurrence and outcome is not known. Both patients who undergo breast-conserving therapy and those who undergo mastectomy should be monitored for the development of new primary cancers in the contralateral breast. The risk of development of a new primary cancer in the contralateral breast after treatment of DCIS is two to five times greater than the risk of development of a first primary breast cancer and is approximately the same as the risk of development of a new contralateral primary cancer after invasive cancer.

Current Management of DCIS at the University of Texas MD Anderson Cancer Center

An algorithm for the current treatment of DCIS at MD Anderson Cancer Center is outlined in Figure 1.3. Annual updates can be found at https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-practice-algorithms/cancer-treatment-algorithms.html. Patients diagnosed with a mammographic abnormality undergo bilateral diagnostic mammography, and the mammograms are compared with previous images, if available. Magnification views are routinely used to delineate the abnormality in the index breast. Ultrasound is also frequently used to assess tumor size, multicentricity, and nodal status. Diagnostic biopsy is performed by using a vacuum-assisted stereotactic core-needle biopsy technique. When DCIS is diagnosed, the pathologic evaluation details the tumor type and grade, any evidence of microinvasion, and the status of both the estrogen and the progesterone receptors. HER2/*neu* amplification or overexpression is not routinely checked, as its presence has unknown clinical significance. MRI is not routinely employed in the preoperative evaluation of patients with DCIS. The decision to use MRI is based on the density of the breasts, findings on mammographic and sonographic imaging, and clinical judgment.

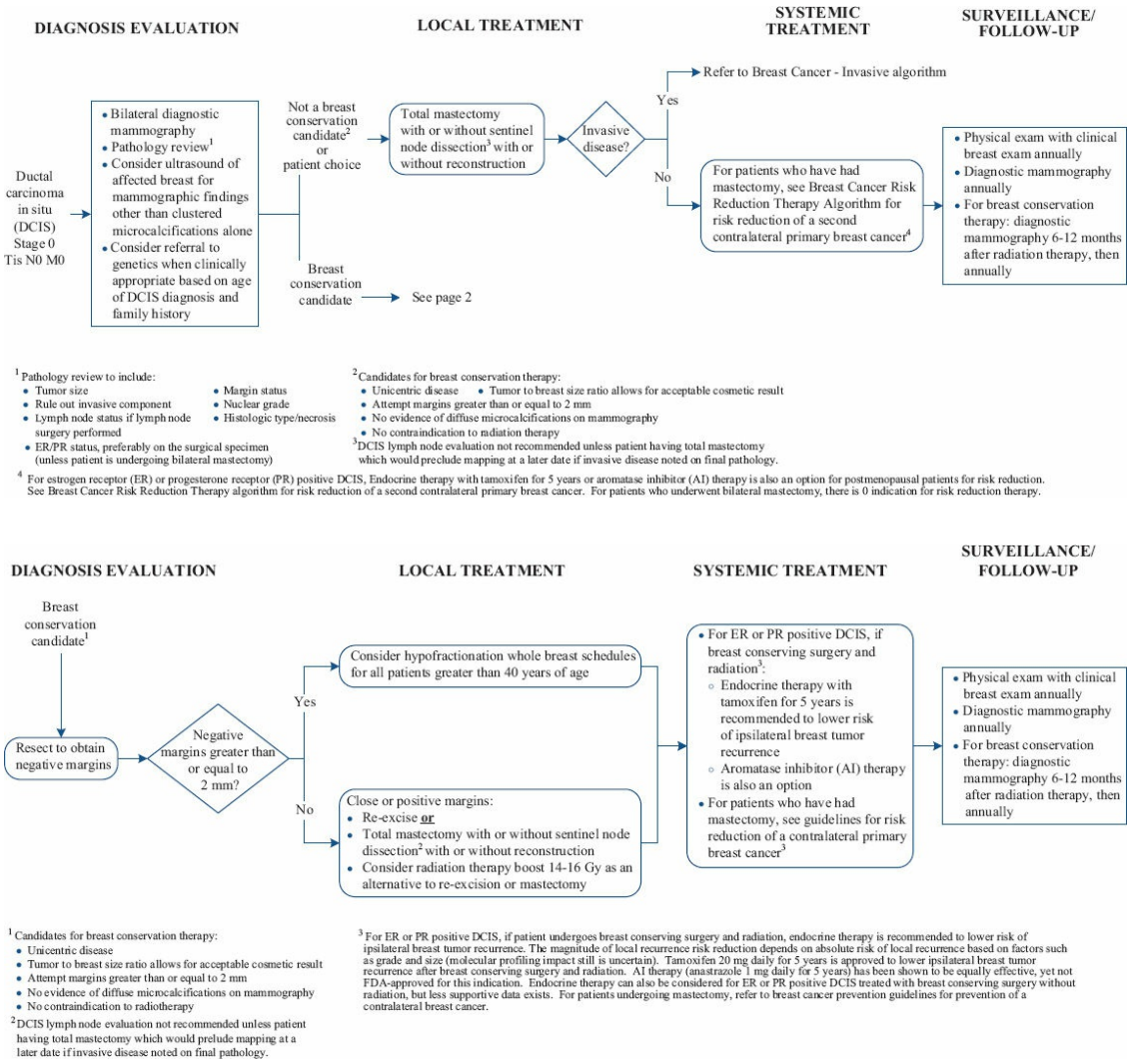


Figure 1.3 Management algorithm of ductal carcinoma in situ (DCIS) at MD Anderson Cancer Center. Pathology review includes tumor size, histologic type, margin status, nuclear grade, and estrogen and progesterone receptor status, as well as ruling out an invasive component. Candidates for breast-conserving surgery are those with unicentric disease, whose ratio of tumor size to breast size allows for an acceptable cosmetic result with resection margins greater than or equal to 2 mm, no evidence of diffuse microcalcifications on mammography, and no contraindications to radiotherapy. Lymph node evaluation for patients with DCIS is not recommended unless patients are planned for total mastectomy which would preclude mapping at a later date if invasive disease noted on final pathology. When available, clinical trials are the preferred option for eligible patients. Copyright 2017 The University of Texas, MD: Anderson Cancer Center.

The choice of surgical therapy for an individual patient is based on

several factors, including tumor size and grade, margin width, mammographic appearance, and patient preference. The benefits and risks of breast-conserving surgery and mastectomy should be discussed in detail with each patient. Most patients with DCIS are candidates for breast-conserving therapy, and this is the preferred method of local treatment since it offers similar overall survival outcomes compared with mastectomy. Mastectomy is indicated in patients with diffuse, malignant-appearing calcifications in the breast and/or persistent positive margins after attempts at surgical excision, and those with a contraindication to postoperative radiation therapy. Although tumor size is not an absolute indication for mastectomy, mastectomy is often preferred for patients with large (>4 cm in diameter), high-grade DCIS. There are few data available on the efficacy of breast-conserving surgery for DCIS with index lesions greater than 4 cm in diameter. Mastectomy may also be a better choice when a patient's anxiety over the possibility of recurrence outweighs the impact a mastectomy would have on her quality of life. Immediate breast reconstruction should be considered for all patients who require or elect mastectomy. Intraoperative margin assessment with sectioned-specimen radiography is used in patients undergoing breast-conserving surgery and for patients with extensive calcifications undergoing skin-sparing mastectomy. Reexcision is usually recommended for patients who have margins less than 2 mm on final pathologic examination after breast-conserving surgery.

Patients who undergo mastectomy for DCIS routinely undergo intraoperative lymphatic mapping and SLN dissection. In patients who undergo breast-conserving surgery, SLN dissection is performed on an individual basis and primarily reserved for cases where the DCIS is palpable, is high grade, or exhibits comedo-type necrosis.

Adjuvant radiation therapy is recommended to reduce the risk of local recurrence in patients who undergo breast-conserving surgery. Breast-conserving surgery alone (without radiation therapy) is considered for select patients with small (<1 cm in diameter), low-grade lesions that have been excised with margins of at least 5 to 10 mm, occur in women of advanced age with short (<15-year) life expectancy, and can be observed diligently for recurrence. Partial breast irradiation is offered for selected patients. Tamoxifen is offered for 5 years to women with ER+ DCIS who do not have a history of venous thromboembolism or stroke.

Following surgical resection, patients undergo annual physical and

clinical breast examinations. Patients who receive breast-conserving surgery and radiation therapy undergo a diagnostic mammogram after surgery to ensure removal of all suspicious calcifications, 6 months after the completion of radiation therapy and annual bilateral mammograms thereafter. If a mastectomy is performed, the patient is followed with an annual diagnostic mammography of the contralateral breast.

HIGH-RISK PREMALIGNANT CONDITIONS

The multistep model for breast carcinogenesis suggests that invasive carcinomas arise from preinvasive "hyperplastic" and neoplastic proliferations. These early proliferative lesions have taken on greater significance as a result of the mammographic screening and detection programs. Pathologists are encountering these proliferative lesions with increasing frequency, and this has highlighted deficiencies in classification systems as well as a lack of data on natural history, making clinical management a challenge.

LOBULAR NEOPLASIA: LOBULAR CARCINOMA IN SITU AND ATYPICAL LOBULAR HYPERPLASIA

LCIS was first described in 1941. During the era that followed, the treatment of LCIS was the same as that of invasive carcinoma: radical mastectomy. Haagensen et al. (1978) is credited with altering the treatment philosophy for LCIS. In a review of 211 cases, a 17% incidence of subsequent invasive carcinoma was found among women with LCIS treated by observation alone (without surgery). The risk of developing a subsequent carcinoma was equal for both breasts, and only six patients died of breast cancer. Haagensen concluded that close observation for LCIS allowed for early detection of subsequent malignancy, with associated high cure rates. Haagensen's rationale for observation of LCIS was based on his view that patients with LCIS were at increased risk for invasive breast cancer but that LCIS itself did not progress into a malignancy.

Today, LCIS is not considered a preinvasive lesion but rather an indicator for increased breast cancer risk of approximately 1% per year, or approximately 20% to 30% at 15 years (Anderson, 2006). The cancer that develops may be invasive ductal or lobular and may occur in either breast. It is, in many instances, multicentric or multifocal as well as bilateral, with

LCIS identified in the contralateral breast in anywhere from 30% to 90% of cases.

Epidemiology

The incidence of LCIS is difficult to estimate because the diagnosis is most often made as an incidental finding. LCIS is often not detectable by palpation, gross pathologic examination, or mammography. On evaluation of mammographic abnormalities, LCIS is found in 0.5% to 1.3% of breast core-needle biopsy specimens and 0.5% to 3.9% of excisional breast biopsy specimens. Traditionally, LCIS was more commonly reported in premenopausal women than in postmenopausal women. In Haagensen's series, 90% of the patients were premenopausal. However, in a review of the Surveillance, Epidemiology, and End Results program database, Li et al. (2002) reported that from 1978 to 1998, the incidence of LCIS increased in all age groups, but it increased the most in women 50 to 79 years old. The reason for this increase in LCIS seen in women 50 years of age or older is multifactorial. Increased use of screening mammography led to an increased number of biopsies performed, increasing the identification rate of LCIS. Furthermore, as estrogen is hypothesized to play a role in the pathogenesis of LCIS, hormone replacement therapy in postmenopausal women may also account for the increased incidence of LCIS in this age group.

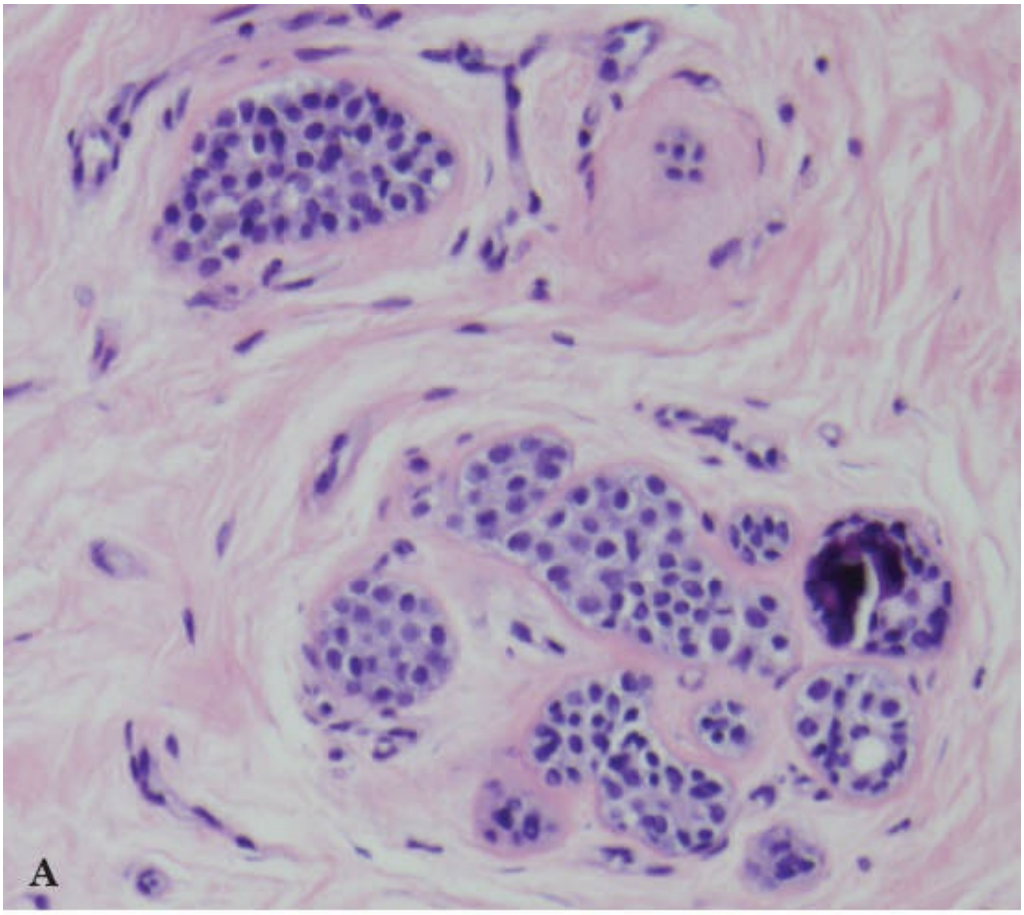
The theory that LCIS represents a marker of increased risk of invasive breast carcinoma is supported by the fact that the mean age at diagnosis is 10 to 15 years younger than that for invasive cancer. However, in women 50 years of age or older, as the incidence of LCIS has increased, the incidence of infiltrating lobular carcinoma has increased concurrently in this age group, whereas women younger than 50 years old have not experienced an increase in invasive lobular carcinoma.

Pathology

LCIS is characterized by intraepithelial proliferation of the terminal ductal–lobular unit (TDLU), but the proliferating cells do not penetrate the basement membrane. Lobular architecture is maintained in LCIS, but all acini are distended and the cells are monomorphic with uniform nuclei containing evenly dispersed chromatin, have a low cytoplasm-to-nucleus ratio, and are only loosely cohesive with a high nucleus-to-cytoplasmic

ratio. Calcifications, mitoses, and necrosis are rare. In ALH, as opposed to LCIS, not all of the acini are abnormal or all of the acini are involved but not all of them are distended, and there may be residual lumina (Fig. 1.4).

Pleomorphic LCIS—which has larger, polymorphic nuclei, central necrosis, more abundant, eosinophilic cytoplasm, and calcifications on histologic examination—is a more recently discovered variant that is more likely to progress to invasive disease and is treated more like DCIS.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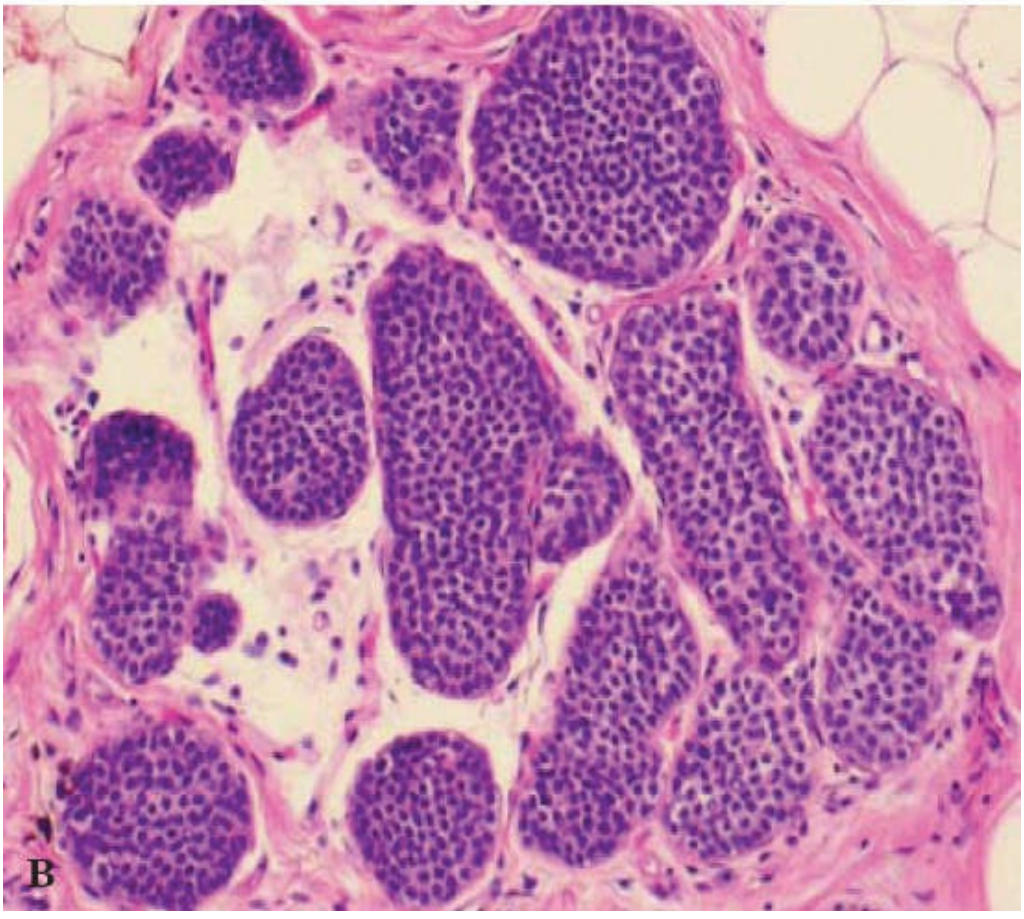
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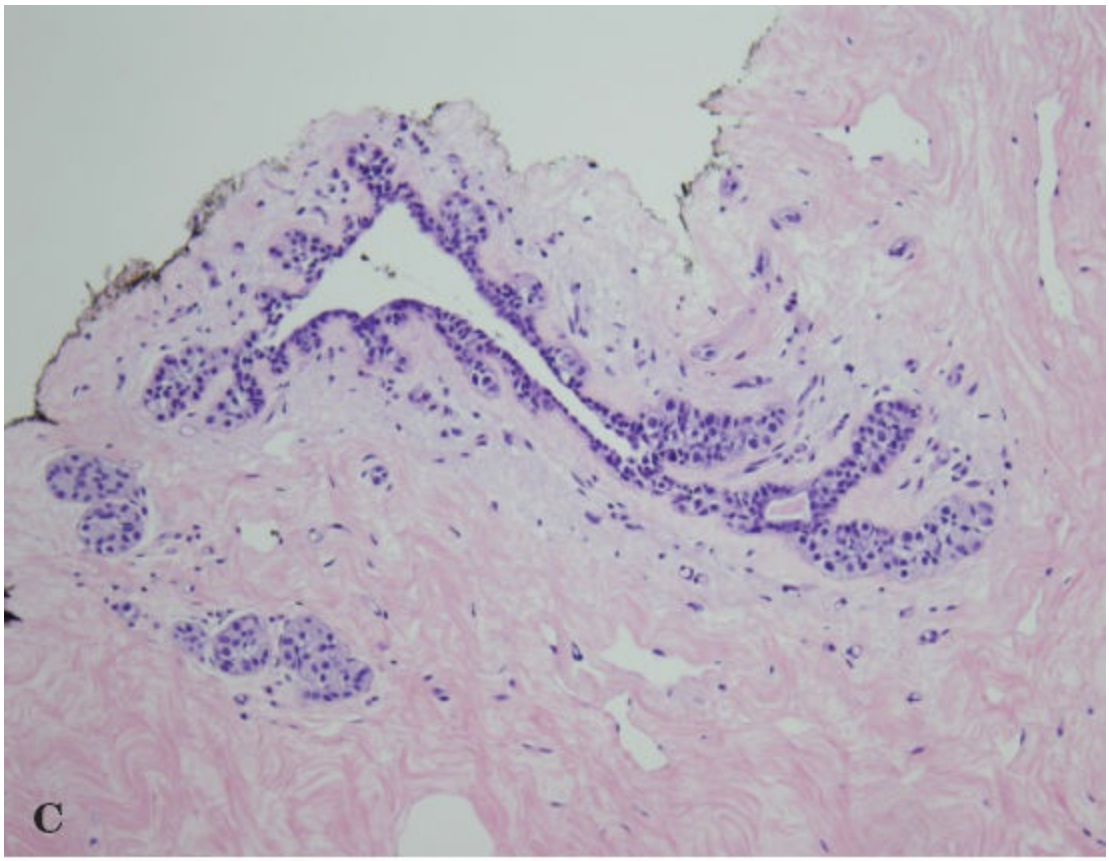
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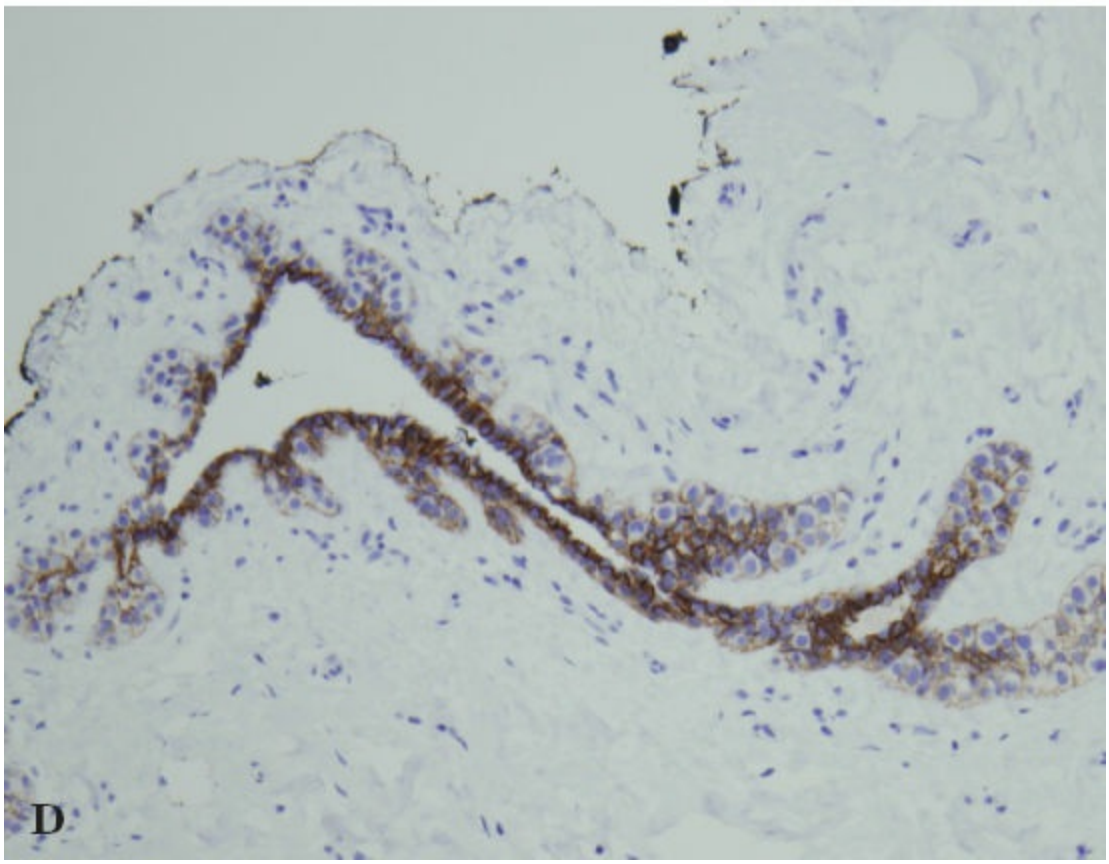
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Figure 1.4 Lobular neoplasia. Lobular neoplasia cells are characterized by small round nuclei with diffuse chromatin pattern and scant cytoplasm. The classification into atypical lobular hyperplasia (ALH) versus lobular carcinoma in situ (LCIS) is based on the extent of involvement and expansion of lobular units. In ALH, lobular units are not expanded (**A**) in contrast LCIS expands lobular units (**B**). Lobular neoplasia cells typically show pagetoid extension into adjacent ducts (**C**). Immunohistochemical staining shows lack of E-cadherin staining in lobular neoplasia cells (**D**).

Molecular analysis of LCIS and invasive lobular carcinoma has revealed decreased expression or complete loss of the cell surface adhesion molecule E-cadherin, which can be stained for on pathology slides to distinguish between borderline DCIS and LCIS. LCIS and invasive ductal carcinoma have in common a similar loss of heterozygosity.

The diagnosis of LCIS involves the differentiation of LCIS from other forms of benign disease and from invasive lesions. Papillomatosis in the terminal ducts may resemble LCIS but lacks the characteristic involvement of the acini. DCIS may extend retrograde into the acini, but it has a more characteristic anaplastic cell morphology and generally expresses E-cadherin. LCIS is contained within the basement membrane and is thus distinguished from invasive lobular carcinoma. In the absence of complete replacement of the lobular unit, ALH is the designated pathologic term.

Taken together, ALH and LCIS constitute a pathologic spectrum known as lobular neoplasia. Historically, ALH was thought to have a weaker association with malignancy, but a recent study suggested that both ADH and ALH confer equal levels of risk, with both markers being associated with an approximately 4.5 times increased risk of invasive breast cancer (Hartmann, 2014). In contrast, LCIS increases the risk of invasive breast cancer by a factor of 7 to 12.

Diagnosis

Clinical Presentation

Because neither LCIS nor ALH is usually detectable by physical examination or mammography, they are most commonly diagnosed as incidental findings in a breast biopsy specimen. Therefore, the clinical presentation of patients with lobular neoplasia is similar to that of patients requiring breast biopsy for fibroadenoma, benign ductal disease, DCIS, or

invasive breast cancer. Patients diagnosed with lobular neoplasia should undergo bilateral diagnostic mammography to exclude other abnormalities in the breast. Ultrasound is also useful in evaluating suspicious findings.

Treatment

Treatment options are (1) lifelong surveillance, (2) bilateral total mastectomies with immediate reconstruction for selected women with a strong family history after appropriate counseling, or (3) pharmacologic risk reduction with anti-estrogen treatment.

Surgery

In the past, many surgeons opted to observe such patients because a diagnosis of LCIS was considered a marker for increased risk of breast cancer rather than a precursor of invasive cancer. However, studies by Arpino et al. (2004) and others have reported a 0% to 10% risk of synchronous invasive breast cancer and a 0% to 50% risk of synchronous DCIS in patients diagnosed with LCIS by core-needle biopsy specimens. Furthermore, multifocal or extensive (>4 TDLUs) LCIS is associated with an increased risk of synchronous invasive cancer. Hence, patients with LCIS that is extensive; an aggressive variant such as pleomorphic, signet cell, macroacinar, or necrotic; or associated with other high-risk features should undergo surgical excision with negative margins in order to rule out (and potentially treat) synchronous invasive cancer and DCIS. Indeed, the most recent NCCN guidelines continue to recommend surgical excision for all LCIS diagnosed on core-needle biopsy. However, ALH and low-risk LCIS that is well sampled—as indicated by the number of vacuum-assisted cores obtained, the gauge of the needle used, and what percentage of any associated calcifications are no longer visible on postbiopsy imaging—do not necessarily warrant surgical excision. At MD Anderson, it is our practice to discuss proliferative benign lesions such as ALH and LCIS in a weekly conference attended by surgeons, pathologists, radiologists, and internists with expertise in cancer prevention and risk reduction. After multidisciplinary discussion and review, it is often determined that asymptomatic, low-risk lesions can either be observed closely with high-risk surveillance (e.g., mammogram and MRI annually or mammogram and MRI obtained in an alternating fashion every 6 months) or treated with anti-estrogen therapy. If incidentally discovered lobular neoplasia has not been well sampled and/or is associated with a

residual mass, calcifications, or symptoms, excisional biopsy is appropriate.

Endocrine Therapy and Risk Reduction

Another treatment option for patients with a diagnosis of lobular neoplasia is pharmacologic risk reduction (previously known as chemoprevention) with hormonal therapy. In the NSABP P-1 breast cancer prevention trial, which was implemented in 1992, Fisher et al. (1998) observed a 56% decrease in the incidence of invasive breast cancers in a subset of women with LCIS who received tamoxifen as compared with women with LCIS who underwent observation alone (RR 0.44, CI 0.16–1.06, $p < 0.01$) and an 86% reduction in invasive breast cancer risk among women with atypia who took tamoxifen (RR 0.14, CI 0.03–0.47, $p < 0.01$). In the NSABP P-2 trial, postmenopausal women with LCIS and atypical hyperplasia were eligible to be randomized to either tamoxifen or raloxifene. Vogel et al. (2006) reported that the two agents offered an equivalent risk reduction for invasive breast cancer (incidence 4.30 per 1,000, vs. 4.41 per 1,000, for tamoxifen and raloxifene, respectively). Patients receiving raloxifene had a lower risk of thromboembolic events and cataracts. There was no statistical difference in risk of other cancers, fractures, ischemic heart disease, and stroke for the two drugs. Updates in 2010 and 2015 revealed that raloxifene was 78% and 81%, respectively, as effective as tamoxifen over time at preventing invasive disease in patients with LCIS and atypical hyperplasia, but had far fewer toxicities, with statistically significantly fewer endometrial cancers. Vogel et al. concluded that depending on an individual's personal risk factors, both raloxifene and tamoxifen are valuable for breast cancer risk reduction in patients with lobular neoplasia and ADH. Raloxifene may be particularly beneficial to a postmenopausal woman with an intact uterus who also faces a risk of osteoporosis; tamoxifen would be an appropriate choice for high-risk postmenopausal women.

The NCIC Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3) was an international, randomized, double-blind, placebo-controlled trial designed to detect a 65% reduction in risk of breast cancer among postmenopausal women with a Gail risk score of 1.7% or higher (i.e., at least a 1.7% risk of breast cancer in the subsequent 5 years) through use of the aromatase inhibitor exemestane with or without the COX-2 inhibitor celecoxib (Goss, 2011). Patients were enrolled between

2004 and 2010 and were initially randomized to one of three arms: 25 mg of exemestane plus placebo daily, 25 mg of exemestane plus celecoxib daily, or placebo plus placebo pills daily. After an unexpectedly high number of cardiovascular events, celecoxib was removed from the protocol, leaving just two arms: exemestane versus placebo. Exemestane provided a 65% reduction in risk of invasive breast cancer (RR 0.35, CI 0.18–0.70, p = 0.002) but did not provide a statistically significant reduction in risk of noninvasive breast cancer. As a result, exemestane, in addition to raloxifene, is now considered an acceptable choice for pharmacologic risk reduction among postmenopausal women with proliferative breast lesions that put them at higher risk for breast cancer.

ATYPICAL DUCTAL HYPERPLASIA

ADH is a proliferative lesion that lies on the spectrum between usual ductal hyperplasia and low-grade DCIS and is associated with an elevated risk of breast cancer.

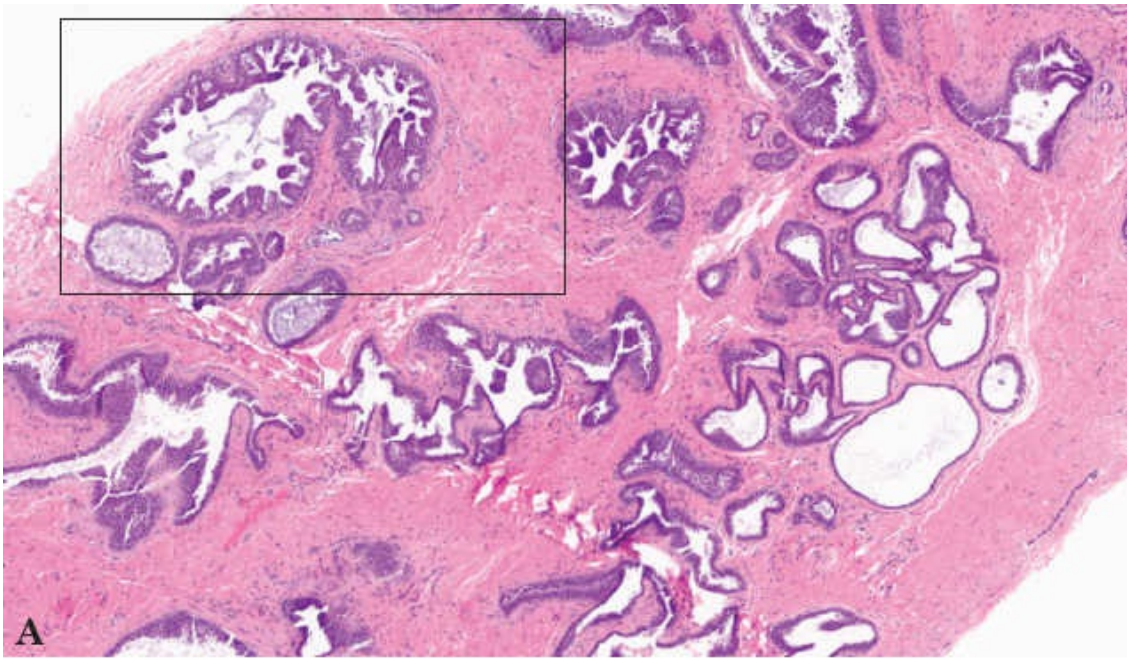
Epidemiology

ADH is found in approximately 5% to 10% of benign breast biopsies and increases the likelihood of future breast cancer by a factor of 4 to 5 (Hartmann, 2014; Hartmann, 2015). Although ADH has long been assumed to be a direct precursor of DCIS and subsequently invasive ductal carcinoma, a recent longitudinal study from the Mayo Clinic points toward its having a role in breast cancer development that is more akin to that of ALH. In the study, subsequent ipsilateral breast cancer occurred at twice the rate of contralateral breast cancer for both ADH and ALH, pointing toward the likelihood that both forms of atypia not only serve as precursors of invasive disease but may also be pathologic biomarkers representing the premalignant potential of the surrounding tissue bed and of both breasts in an affected individual. Atypical hyperplasia is associated with a 30% 25-year cumulative incidence of breast cancer (invasive or noninvasive).

Pathology

On pathologic assessment, ADH fulfills some but not all of the criteria for a diagnosis of low-grade DCIS (Fig. 1.5). Quantitatively, ADH is defined as involving fewer than 2 TDLUs and occupying an area of less than 2 mm

in diameter. It consists of monotonous, round, cuboidal, or polygonal cells arranged in a regular pattern, with rare mitoses and evenly distributed nuclei. However, in contrast to DCIS, there is retention of normal epithelium in parts of the duct. Cribriform-like secondary lumens, micropapillary formations, and necrotic patterns may be observed. It tends to be strongly ER+ and PR+, like lobular neoplasia and low-grade DCIS, and is rarely HER2/*neu*-amplified.



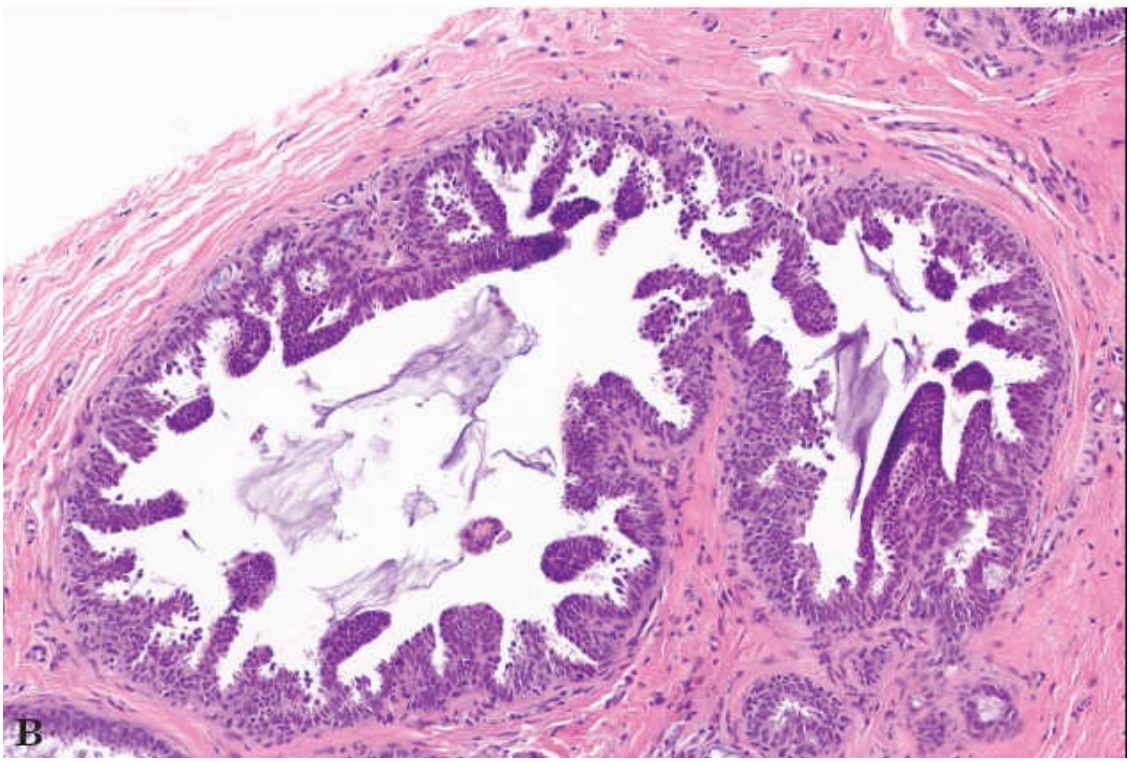


Figure 1.5 Atypical ductal hyperplasia (ADH). Intraductal proliferation of monotonous cells with cribriform and micropapillary features involving a single duct (**A**). Higher magnification of the duct within the frame showing uniformity of the proliferating cells with cytologic features consistent with low-grade ductal carcinoma in situ (**B**). Based on focal involvement and small size of the lesion (less than 1 mm) it is classified as ADH.

Diagnosis

Clinical Presentation

As with lobular neoplasia, ADH is often diagnosed as an incidental finding in the specimen from a breast biopsy performed for symptoms or as part of the work up of an abnormal finding on radiographic screening. If not already performed, bilateral diagnostic mammogram and, if necessary, ultrasound should be performed once ADH is found.

Treatment

Because one of the pathologic criteria for differentiating ADH from DCIS is size, formal exclusion of DCIS cannot be confirmed on core-needle biopsy. Furthermore, an estimated 25% to 30% of cases of ADH are found to be associated with DCIS on surgical excision. Accordingly, excisional biopsy is warranted for ADH found on core-needle biopsy.

As discussed before, proliferative benign lesions such as ADH are discussed at MD Anderson in a weekly multidisciplinary conference at which it is sometimes determined that asymptomatic, well-sampled, low-risk lesions can either be observed with imaging surveillance or treated with anti-estrogen therapy. As discussed above, NSABP P-1 demonstrated an 86% reduction in risk of future invasive breast cancer among women with atypia (including ALH and ADH) who took tamoxifen, while NSABP P-2 and MAP.3 demonstrated the efficacy of raloxifene and exemestane, respectively, as risk-reducing agents in postmenopausal women with ADH and ALH.

The most recent guidelines from the American Society of Clinical Oncology (ASCO) and NCCN recommend consideration of pharmacologic risk reduction with tamoxifen for premenopausal women and raloxifene or exemestane for postmenopausal women in women with a 5-year absolute risk of breast cancer greater than or equal to 1.7%, a

criteria that is met by women with ADH, ALH, and LCIS. However, only a minority of women who meet these criteria are counseled about these medications and an even smaller proportion are ever prescribed or initiated on these treatments. Surgeons can be important modulators of this risk-prevention strategy and should seek opportunities to counsel appropriate patients with high-risk proliferative lesions and to encourage their enrollment in clinical trials as appropriate and available.

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2 Invasive Breast Cancer

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INTRODUCTION

Invasive breast malignancy is a systemic disease. Over the past several decades breast cancer management has changed dramatically, evolving from primarily surgical therapy to a multidisciplinary approach with improved understanding of tumor biology and emphasis on personalized care and specialized techniques. Surgical therapy and decision making is embedded within the context of multidisciplinary care. This chapter will comprehensively review contemporary practice, diagnosis and management of invasive breast cancer.

EPIDEMIOLOGY

Breast cancer remains the most common cancer diagnosed and the second most common cause of cancer-related mortality among women in the United States. The American Cancer Society estimates that in 2016, approximately 246,660 new cases of invasive breast cancer will be diagnosed and nearly 40,450 breast cancer related deaths will occur. Currently, the lifetime risk of breast cancer among women is 1 in 8 or 12% compared to 1 in 11 for women in the 1970s. This increase in risk over the past four decades is attributed to longer life expectancy, changes in reproductive patterns, hormone use, the rising prevalence of obesity, as well as increased detection through screening mammography. Although the incidence of breast cancer has risen, breast cancer mortality has decreased. Breast cancer death rates have decreased 36% from 1989 to 2012, after slowly increasing (0.4% per year) since 1975. This likely reflects the increased use of screening mammography beginning in the early 1980s leading to detection of earlier stage disease, as well as continued improvements in systemic adjuvant therapy.

Breast cancer incidence rates are highest in non-Hispanic white women,

followed by African American women and are lowest among Asian/Pacific Islander women. Contrastingly, breast cancer death rates are highest for African American women, followed by non-Hispanic white women, and are lowest for Asian/Pacific Islander women. Furthermore, the difference in long-term breast cancer mortality by race/ethnicity persists and is increasing with breast cancer death rates 42% higher in African American than Caucasian women in 2012. This disparity reflects a combination of factors, including differences in stage at diagnosis, obesity, comorbidities, tumor characteristics, screening, access, adherence, and response to treatment.

RISK FACTORS

Contemporary breast cancer care increasingly relies on a personalized multidisciplinary approach to treatment. In order to provide individual counseling of risk, several risk assessment models are available. The most important risk factor for the development of breast cancer is gender. The female-to-male ratio for breast cancer is 100:1. Therefore, this section focuses on risk factors among women.

Multiple additional factors are associated with an increased risk of developing breast cancer, including age, genetic predisposition, a history of proliferative breast disease, prior radiation exposure, a personal or family history of breast cancer, and hormone exposure. A simplified version of previously summarized risk factors for breast cancer is provided in Table 2.1.

TABLE 2.1 Risk Factors for Breast Cancer and Associated Relative Risks

Risk Factor	Category at Risk	Relative Risk
Germline mutations	*BRCA1* and younger than 40 years old	200
	BRCA1 and 60–69 years old	15
Proliferative breast disease	Lobular carcinoma in situ	16.4
	Ductal carcinoma in situ	17.3
Personal history of breast cancer	Invasive breast cancer	6.8
Ionizing radiation exposure	Hodgkin disease	5.2
Family history	First degree relative with premenopausal breast cancer	3.3
	First degree relative with postmenopausal breast cancer	1.8
Age at first childbirth	Older than 30 years	1.7–1.9
Hormone replacement therapy with estrogen and progesterone	Current user for at least 5 years	1.3
Early menarche	Younger than 12 years	1.3
Late menopause	Older than 55 years	1.2–1.5

From Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003;237:474–482, with permission.

Age

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the incidence of breast cancer increases rapidly during the fourth decade of life. After menopause, the incidence continues to increase but at a much slower rate, peaking in the fifth and sixth decades of life and slowly leveling off during the sixth and seventh decades. Approximately one out of eight invasive breast cancers will be found in women younger than 45 years and approximately two-thirds of invasive breast cancers are found in women older than 55 years.

Personal and Family History of Breast Cancer

A strong family history of breast cancer has been recognized to increase a woman's risk of breast cancer. The overall risk depends on the number of relatives with breast cancer, their ages at diagnosis, and whether the disease was unilateral or bilateral. The highest risk is associated with a young first-degree relative with bilateral breast cancer. Overall, the risk of developing breast cancer is increased approximately 1.5- to 3-fold if a woman has a first degree relative (mother or sister) with breast cancer. A personal history of breast cancer is a significant risk factor for the development of cancer in the contralateral breast with an estimated risk of approximately 0.5% to 1% per year of follow-up.

Genetic Predisposition

Hereditary breast cancer secondary to genetic mutations account for 5% to 10% of all breast cancer. Several mutations have been identified to have an increased association with breast cancer risk although to varying degrees. These include *BRCA1*, *BRCA2*, PALB2, CHEK2, p53 (Li–Fraumeni syndrome), PTEN (Cowden disease), ATM, CDH1, STK11 (Peutz–Jeghers syndrome) and Lynch syndrome. Expanded panel genetic testing is becoming increasingly common although the penetrance of these mutations and relative risk of breast cancer may vary. Testing of an affected family member is recommended to identify and direct testing for a specific genetic loci mutation in unaffected family members. Genetic testing should be preceded by genetic counseling (Table 2.2).

TABLE 2.2 Common Genetic Mutations Associated with Breast Cancer

	Mutation	Associated Risk
BRCA1	Chromosome 17q	Malignancies of the breast, ovaries, and possibly prostate and colon
BRCA2	Chromosome 13q	Malignancies of the breast (including male), ovaries, prostate, larynx, and pancreas
Li–Fraumeni	p53 gene on chromosome 17p	Malignancies of the breast, brain, and adrenal glands; soft-tissue sarcomas
Cowden disease	Mutation in the *PTEN* gene on chromosome 10q	Malignancies of the breast, colon, uterus, thyroid, lung, and bladder; hamartomatous polyps in GI tract
Peutz–Jeghers	Mutation in the *STK11* gene on chromosome 19p	Malignancies of the breast and pancreas; mucocutaneous melanin deposition, hamartomas of the GI tract

The most widely studied and known mutations are in the BRCA 1 and 2 genes. BRCA1 mutations have an estimated lifetime risk of breast cancer of 57% to 65%, and are also associated with risk of ovarian, fallopian tube, peritoneal, and pancreatic cancers, in addition to Fanconi anemia, a syndrome that is associated with childhood solid tumors and development of acute myeloid leukemia. BRCA2 mutation carriers have an estimated

breast cancer lifetime risk of 45% to 55% in addition to the risk of ovarian, pancreatic, prostate, and higher association with male breast cancers. BRCA1 and 2 mutation carriers are encouraged to undergo high-risk screening with annual mammogram alternating with breast MRI or prophylactic mastectomy for risk-reduction.

Proliferative Breast Disease

Nonproliferative breast diseases such as adenosis, fibroadenomas, apocrine changes, duct ectasia, and mild hyperplasia are not associated with an increased risk of breast cancer. However, proliferative breast diseases are associated with breast cancer to various degrees (RR is 1.5 to 2). Moderate or florid hyperplasia without atypia, papilloma, and sclerosing adenosis carry a slightly increased risk of breast cancer, 1.5 to 2 times that of the general population. Atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) are associated with a four- to fivefold increased risk of developing breast cancer in either breast. Lobular carcinoma in situ (LCIS) is associated with up to an eight- to tenfold risk of breast cancer. Risk factor modification with chemoprevention in the setting of high-risk lesions is highly effective as evidenced by the findings of the NSABP P2 trial. This study found chemoprevention with tamoxifen or raloxifene was associated with a significant decrease in the incidence of invasive and noninvasive breast cancer in the setting of ADH and LCIS. Therefore, consideration of chemoprevention and risk assessment strategies for patients with high-risk lesions should be strongly encouraged.

Radiation Exposure

Therapeutic radiation exposure to treat disease can be a significant cause of radiation-induced carcinogenesis. The highest associated risk is seen with higher doses of radiation and radiation treatment given at a young age, particularly before age 30 (relative risk is 5.2). This has been observed in women receiving mantle irradiation for treatment of Hodgkin disease. Given the elevated lifetime risk of breast cancer in this population high-risk screening with annual mammography and breast MRI is recommended.

Endogenous Hormone Exposure

The hormonal milieu at different times in a woman's life may affect her risk of breast cancer and the total duration of exposure to endogenous estrogen is an important factor in breast cancer risk. Increased risk has been associated with early age at menarche, establishment of regular ovulatory cycles, nulliparity, advanced age at first childbirth and late menopause. Interestingly, women who have their first child between ages 30 and 34 have the same risk as nulliparous women whereas women older than 35 years have a greater risk than nulliparous women.

Exogenous Hormone Exposure

Exogenous hormone replacement therapy is known a risk factor for breast cancer. The Women's Health Initiative, a large-scale prospective study, was abruptly halted in 2002 after interim analysis indicated hormonal replacement therapy (HRT) was associated with a 26% increase in the risk of breast cancer over a 5-year period as well as an increased risk of stroke and coronary artery disease. Described benefits associated with HRT include increased bone density and fewer postmenopausal symptoms, make ongoing use attractive for many women. A recent meta-analysis from the Mayo Clinic by Benkhadra et al., looked at 43 randomized controlled trials and found no association between the use of HRT and cardiac death or stroke. Estrogen plus progesterone use was associated with a likely increase in breast cancer mortality (RR 1.96 [95% CI 0.98–3.94]), whereas estrogen alone use was not. In women started at an earlier age on HRT (age less than 60 years), there was a reduction in all-cause mortality including cardiovascular and cancer deaths. Overall, the current evidence suggests that HRT does not affect the risk of death from all causes, cardiac death and death from stroke or cancer. Therefore, treating physicians should thoroughly discuss the risks and benefits of this therapy with their patients.

Risk Assessment Tools

A number of models exist that assess the risk of developing breast cancer. The Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool/) is a publicly available resource that was developed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP). It is based on a statistical model known as the GAIL model. This model

incorporates a woman's personal medical history (number of previous breast biopsies and the presence of atypia in those biopsies), reproductive history (age at the start of menstruation and age at the first live birth) and the history of breast cancer among her first-degree relatives (mother, sisters, daughters) to estimate her risk of developing invasive breast cancer over a 5-year period and over her lifetime.

The appropriate risk assessment tool should be chosen based on a patient's specific risk factors. For example, while the Gail model is appropriate for women with a history of atypia, it is not applicable to women with a BRCA mutation. In these patients, the BRCAPRO model is more informative. The Tyrer–Cuzick model can better predict risk in patients with an extensive family history that would be underestimated by other models.

Pathology

Invasive carcinomas of the breast tend to be histologically heterogeneous tumors. The vast majority are adenocarcinomas that arise from the terminal ductal lobular units. There are five common histologic variants of mammary adenocarcinoma.

1. *Invasive ductal carcinoma* accounts for 75% of all breast cancers. This lesion is characterized by the absence of special histologic features. It is firm on palpation and gritty when transected. It is associated with various degrees of fibrotic response. Often there is associated ductal carcinoma in situ (DCIS) within the specimen. Invasive ductal carcinomas may metastasize to axillary lymph nodes. The prognosis for patients with these tumors is poorer than that for patients with some of the other histologic subtypes (i.e., mucinous, colloid, tubular, and medullary). Distant metastases are found most often in the bones, lungs, liver, and brain.
2. *Invasive lobular carcinoma* accounts for 5% to 10% of breast cancers. Clinically, this lesion often has an area of ill-defined thickening within the breast. Microscopically, small cells in a single- or Indian-file pattern are characteristically seen. Invasive lobular cancers tend to grow around ducts and lobules. Multicentricity and bilaterality are observed more frequently in invasive lobular carcinoma than in invasive ductal carcinoma. The prognosis for invasive lobular carcinoma is similar to that for invasive ductal carcinoma. In addition to metastasizing to axillary lymph nodes,

invasive lobular carcinoma is known to metastasize to unusual sites (e.g., meninges and serosal surfaces) more often than other forms of breast cancer.

3. *Tubular carcinoma* accounts for only 2% of breast carcinomas. The diagnosis of tubular carcinoma is made only when more than 75% of the tumor demonstrates tubule formation. Axillary nodal metastases are uncommon with this type of tumor. The prognosis for patients with tubular carcinoma is more favorable than that for patients with other types of breast cancer.
4. *Medullary carcinoma* accounts for 5% to 7% of breast cancers. Histologically, the lesion is characterized by poorly differentiated nuclei, a syncytial growth pattern, a well-circumscribed border, intense infiltration with small lymphocytes and plasma cells, and little or no associated DCIS. The prognosis for patients with pure medullary carcinoma is favorable however, mixed variants with invasive ductal components will have prognoses similar to invasive ductal carcinoma.
5. *Mucinous or colloid carcinoma* constitutes approximately 3% of breast cancers. It is characterized by an abundant accumulation of extracellular mucin surrounding clusters of tumor cells. Colloid carcinoma is slow growing and tends to be bulky. These tumors are associated with a favorable prognosis.
6. *Rare histologic types* of breast malignancy include papillary, apocrine, secretory, squamous cell and spindle cell carcinomas, and metaplastic carcinoma. Invasive ductal carcinomas occasionally have small areas containing one or more of these special histologic types. Tumors with these mixed histologic appearances behave similarly to pure invasive ductal carcinomas.

Breast Cancer Molecular Subtypes

Perhaps one of the most striking advances in breast cancer management and understanding came with the molecular profiling of breast cancer characterizing four distinct subtypes based on the landmark paper by Perou et al., in 2000. These define tumor biology and correlate with outcome and are broadly described as luminal A, luminal B, HER2 enriched, and basal like according to the most common profiles for each subtype. However, not all tumors within each subtype contain all features. The estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor are used as surrogates to approximate these subtypes and guide clinical care and

management decisions (Table 2.3).

Luminal A: most (74%) of breast cancers express the estrogen receptor (ER+) and/or the progesterone receptor (PR+) but not HER2 (HER2−). These cancers tend to be more indolent than other subtypes. Luminal A tumors are associated with the most favorable prognosis, particularly in the short term, in part because expression of hormone receptors is predictive of a favorable response to hormonal therapy.

TABLE 2.3 Breast Cancer Molecular Subtypes

Subtype[a]	Typical Histopathologic Features
Luminal A	ER-positive and/or PR-positive HER2-negative Low Ki67
Luminal B	ER-positive and/or PR-positive HER2-positive (or HER2-negative with high Ki67)
Basal-like	ER-negative PR-negative HER2-negative
HER2 enriched	ER-negative PR-negative HER2-positive

[a]Not all tumors within each subtype contain all features.
ER, estrogen receptor; PR, progesterone receptor, HER2, human epidermal growth factor receptor 2.

Luminal B: these breast cancers are ER+ and/or PR+ and are further defined by either HER2 amplification, or high Ki-67 (an indicator of cellular proliferation). They tend to have higher grade and more aggressive features than luminal A breast cancers.

HER2-enriched: these breast cancers produce excess HER2 and do not express hormone receptors. These cancers tend to grow and spread more aggressively than other breast cancers and are associated with poorer short-term prognosis compared to ER+ breast cancers. However, the recent widespread use of targeted therapies for HER2-positive cancers has reversed much of the adverse prognostic impact of HER2 overexpression, with up to 40% of women achieving a pathologic complete response to combination chemotherapy and targeted anti-HER2 therapies.

Basal like: these tumors are more biologically aggressive and are

typically characterized by the lack of the ER, PR and HER2 receptor. These cancers are often found in premenopausal women, those with a BRCA1 gene mutation, and are nearly two times more common in black women than white women in US. The majority (>70%) of triple negative breast cancers fall into the basal-like subtype. Triple negative breast cancers have a poorer short-term prognosis than other breast cancer types, in part because there are currently no targeted therapies for these tumors. However, a proportion of these tumors are very chemosensitive, exhibiting a pathologic complete response in up to a third of patients. Furthermore, several molecular subtypes of triple negative breast cancer have been described. These may provide further insights into the varying biologic response and assist in development of therapeutic targets in addition to chemotherapy.

Diagnosis and Evaluation

The diagnosis of breast cancer has undergone a dramatic evolution over the past 25 years. Previously, the majority of breast cancers were detected by self-examination however, with adoption of mammographic screening, there has been a greater shift toward the diagnosis of nonpalpable lesions. Evaluation of breast cancer relies on comprehensive history and physical examination, radiographic, and tissue diagnosis.

History and Physical Examination

The history is directed at assessing cancer risk and establishing the presence or absence of symptoms indicative of breast disease. It should include age at menarche, menopausal status, previous pregnancies, and use of oral contraceptives or postmenopausal replacement estrogens. A personal history of breast cancer and the age at diagnosis, as well as a personal history of other cancers treated with radiation (e.g., Hodgkin disease) is important. In addition, the family history of breast cancer or ovarian cancer in first-degree relatives should be established. Any significant prior breast history should be elucidated including previous breast biopsies, especially if done for atypical disease, breast augmentation/reduction, breast problems, and any imaging history. After the risk for breast cancer has been determined, the patient should be assessed for specific symptoms. Breast pain and nipple discharge are often, but not always, associated with benign processes such as fibrocystic disease and intraductal papilloma. Malaise, bony pain, and weight loss are

rare but may indicate metastatic disease.

Physical examination by the health care provider should take into consideration the comfort and emotional well-being of the patient. Examination should include careful visual inspection with the patient in the upright and supine positions. Nipple changes, breast asymmetry, and obvious masses are all noted. The skin must be inspected for subtle changes; these can range from slight dimpling to the more dramatic *peau d'orange* (an erythematous and thickened appearance associated with locally advanced or inflammatory breast cancer). In large or ptotic breasts, the breasts should be lifted to facilitate inspection of the inferior portion of the breast and the inframammary fold. After careful inspection and with the patient remaining in the sitting position, the cervical, occipital, and periclavicular nodal basins are examined for potential disease. Both axillae are then carefully palpated. If palpable, nodes should be characterized as to their number, size, and mobility. Examination of the axilla always includes palpation of the axillary tail of the breast as assessment of this area is often overlooked once the patient is placed in a supine position. Palpation of the breast parenchyma itself is accomplished with the patient supine and the ipsilateral arm placed over the head. The subareolar tissues and each quadrant of both breasts are systematically palpated. Masses are noted with respect to their size, shape, location, consistency, and mobility.

Critical analysis of the breast physical examination has shown limitations in differentiating benign and malignant disease, even among experienced examiners. Because of the high rate of inaccuracy, any persistent breast concern requires additional evaluation.

Diagnostic Imaging

The choice of initial diagnostic evaluation after the detection of a breast mass should be individualized for each patient according to age, perceived cancer risk, and characteristics of the lesion. For most patients, mammographic evaluation is the essential initial step, followed by ultrasound.

The American College of Radiology developed the breast imaging reporting and data system (BIRADS), which categorizes mammographic findings as follows:

- BIRADS 0, incomplete or further imaging needed
- BIRADS 1, negative (no findings)
- BIRADS 2, benign appearance

- BIRADS 3, probably benign appearance, short interval follow-up recommended (<2% chance of malignancy)
- BIRADS 4, findings suspicious for breast cancer (20% to 35% chance of malignancy)
  - 4a mildly suspicious
  - 4b intermediately suspicious
  - 4c moderately suspicious
- BIRADS 5, findings highly suspicious for breast cancer (>90% chance of malignancy)
- BIRADS 6, known biopsy proven malignancy

On the basis of these findings, recommendations are made for either short- or long-term surveillance versus further immediate work up. For lesions interpreted as “probably benign” (BIRADS 3) such as well-defined, solitary masses, careful counseling, and short-term follow-up with repeat radiographic studies in 6 months may be undertaken in patients at low risk for breast cancer, whereas a BIRADS 4 reading usually recommends further evaluation with biopsy as indicated. However, if a stellate or spiculated mass typical of malignancy (BIRADS 5) is identified, immediate evaluation with biopsy is required.

Mammography should evaluate both breasts for evaluation of the palpable lesion as well as identifying nonpalpable lesions. Bilateral synchronous cancers occur in approximately 3% of all cases and at least half of these lesions are nonpalpable. Mammographic signs of malignancy include microcalcifications and density changes such as a discrete masses, architectural distortion and focal asymmetry. The most predictive mammographic findings of malignancy are spiculated masses with associated architectural distortion, clustered microcalcifications in a linear or branching array, and microcalcifications associated with a mass. Additional suspicious findings on mammogram include nipple changes and axillary adenopathy. The presence or absence of these mammographic findings can predict malignancy with an accuracy of 70% to 80%. Mammography is least accurate in younger patients with dense breasts and for this reason, it is not commonly used in patients younger than the age of 35 years for screening.

Breast ultrasound is an important adjunct to mammography and assists in clinical decision making. Particularly in young women with dense breast tissue, ultrasound is often used to further evaluate suspicious areas or palpable lesions. For all ages, it is regularly included in the initial

evaluation and work up of mammographically indeterminate lesions, solid and cystic lesions, as well as regional nodal evaluation. Ultrasound is routinely used at the University of Texas M. D. Anderson Cancer Center (MDACC) to evaluate the axillary nodal basin and any suspicious infraclavicular, supraclavicular, or internal mammary adenopathy. Any suspicious nodes are sampled at that time by ultrasound-guided fine-needle aspiration (FNA) or core-needle biopsy with or without placement of a marker clip. Marking the biopsy proven axillary lymph node has increasing importance in the current era of evaluating lymph nodes after neoadjuvant chemotherapy.

Breast MRI has been gaining in popularity for the diagnosis and surgical planning of breast cancer though its utility remains controversial. The increased sensitivity of MRI can lead to over diagnosis, more benign biopsies and is associated with an increased conversion from breast conservation to mastectomy. However MRI is indicated in the following circumstances:

- As an adjunct for evaluating inconclusive findings on conventional imaging
- In the case of nodal or metastatic breast cancer with an unknown primary
- A diagnosis of Paget disease, without mammographically or sonographically identified mass
- To evaluate suspected chest wall invasion of a tumor

MRI is also indicated for high-risk screening in women with a history of mantle radiation, BRCA1 or BRCA2 gene mutation or a documented lifetime risk of breast cancer greater than 20% to 25%. Studies evaluating high-risk patients with an overall cumulative lifetime risk of developing breast cancer of approximately 30% show that MRI is able to detect cancer in approximately 1% to 3% of patients.

Tissue Biopsy

Biopsy for diagnosis should follow radiographic evaluation of suspicious breast lesions. FNA is unable to distinguish between *in situ* and invasive disease and therefore core-needle biopsy is preferred for initial diagnosis. Image guidance is recommended. Palpable lesions may be amenable to ultrasound guided biopsy whereas nonpalpable lesions identified only by mammography are more suitable for stereotactic biopsy. Placement of a marking clip is necessary and confirms the intended lesion was biopsied,

assists in long-term follow-up of benign masses and identifies the location of any malignant lesion for future excision and/or to follow response with neoadjuvant therapy. A postbiopsy mammogram should be performed to ensure proper placement of the marker clip. Biopsy should be deferred until after radiographic examination is completed as a postbiopsy hematoma can obscure subsequent radiographic evaluation. It is imperative that the imaging findings and final pathology are evaluated for concordance in regards to the suspicion of malignancy. In the setting of discordance additional evaluation is necessary to rule out a malignancy.

Excisional Biopsy

Excisional biopsy for the diagnosis of breast cancer has fallen out of favor as the importance of preoperative histopathology increasingly dictates multidisciplinary care and operative planning. Furthermore, advances in radiologic interventions including ultrasound and stereotactic guided biopsy and MRI-guided biopsies, mean that it is rare that a tissue diagnosis cannot be reached percutaneously and excisional biopsy may be needed in only a handful of circumstances. Appropriate uses of excisional biopsy include the following: (1) excision of a high-risk lesion such as ADH or LCIS with mass to rule out an associated cancer, (2) removal of growing or suspicious fibroadenoma to rule out cystosarcoma phyllodes, (3) patient preference due to distortion, pain, or psychological distress, (4) inability to obtain radiographic-guided biopsy, (5) discordance of clinical-pathologic features.

When core-needle biopsy or FNA is impossible or inappropriate, excisional breast biopsy may be performed and serves both diagnostic and local treatment purposes. Careful surgical planning with respect to future breast conserving therapy (BCT) or mastectomy incisions should be considered. Preoperative needle localization with a self-retaining hook wire or radioactive I-125 seed under image guidance is required, as is careful communication between the radiologist and the surgeon. Postlocalization mammograms are reviewed to confirm placement of the wire or seed within the targeted area. Excision is then performed by removing breast tissue around the marker with incisions placed overlying the lesion not at the wire entry site. Postexcision specimen radiographs are essential to confirm excision of the target lesion with marker clip and localization wire or seed.

Meticulous orientation and handling of the specimen is critical. The

specimen should be oriented such that the margins are clearly identified (for example, short stitch superior, long stitch lateral with breast laterality clearly labeled) and when possible, hand delivered to the pathology department for further assessment.

Staging

Following a breast cancer diagnosis, the patient is clinically staged using the American Joint Committee on Cancer (AJCC) guidelines. The AJCC TNM breast cancer staging system was updated in 2017 and published in the eighth edition of the *AJCC Cancer Staging Manual*. TNM classifications and stage groupings are summarized in Tables 2.4 and 2.5. Three major changes were incorporated into the most recent AJCC edition. First, LCIS was removed from the staging system, asserting the belief that it is not a malignancy, but a risk factor. This includes exclusion of pleomorphic LCIS. In disease identified to be a mix of LCIS and DCIS, the case is classified as pTis. Secondly, biologic factors including hormone receptor expression, HER2 amplification, and genomic panels were felt to be as equally important as anatomic descriptors of disease in defining prognosis. Therefore these factors have been incorporated into the AJCC staging, specifically with multigene panel results being identified as stage modifiers. Finally, immunohistochemically detected tumor markers (ER/PR/HER2) are now incorporated into the staging system.

TABLE **2.4** Current AJCC TNM Classification and Stage Grouping for Breast Carcinoma

Classification and Stage Grouping	Definition
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or DCIS
T1	Tumor ≤20 mm greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin; invasion of the derms alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectorails muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satelite nodules and/or edema (including peau d' orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N) Clinical (cN)	
cNX	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastasis
cN1	Metastases to movable ipsilaterial Level I, II axillary lymph node(s)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted, or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastasis
cN2a	Metastasis in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastasis only in ipsilateral internal mammary nodes absence of axillary lymph node metastasis
cN3	Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastasis in ipsilateral infraclavicular lymph node(s)
cN3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Regional Lymph Nodes (N) Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, not removed for pathologic study)
pN0	No regional lymph node metastasis identified or ITCs only

pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph nodes
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction; no ITCs detected
pN1	Metastasis in 1–3 axillary lymph nodes, and/or clinically negative internal mammary nodes with micrometastasis or macrometastasis by sentinel lymph node biopsy
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastasis in ipsilateral internal mammary nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastasis in 4–9 axillary lymph nodes, or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastasis
pN2a	Metastasis in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular (Level III axillary) lymph nodes, or in positive ipsilateral internal mammary lymph nodes by imaging in the *presence* of 1 or more positive Level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and micrometastasis or macrometastasis by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular (Level III axillary) lymph nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging) or pN2a in the presence of pN1b
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0 (i+)	No Clinical or radiographic evidence of distant metastases
M1	Distant metastasis detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

DCIS, ductal carcinoma in situ; IHC, immunohistochemistry; RT-PCR, reverse transcriptase-polymerase chain reaction.
Adapted from the *AJCC Cancer Staging Manual.* 8th ed. AG Switzerland: Springer, Inc.; 2017.

TABLE **2.5** Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1	N1mi	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Adapted from the AJCC Cancer Staging Manual. 8th ed. AG Switzerland: Springer, Inc.; 2017.

Early Stage Breast Cancer

The majority of patients with breast cancer present with tumors less than 5 cm in diameter and no evidence of fixed or matted nodes consistent with clinical stage I or II disease. Workup for patients with clinical stage I or stage II breast cancer is usually limited to a complete history and physical examination, a chest radiograph, and evaluation of serum liver chemistries. The routine use of systemic staging in asymptomatic patients is not generally indicated (See Figures 2.1 to 2.4).

The treatment approach consists of local regional therapy with surgery and radiation therapy when indicated. Surgical options include breast conservation therapy including segmental mastectomy followed radiation therapy or total mastectomy with or without reconstruction. Sentinel lymph node dissection is standard practice for axillary staging. Systemic therapy in the neoadjuvant or adjuvant setting is indicated as many patients may harbor micrometastatic disease. The systemic therapy options are formulated based on patient related factors, tumor related factors including receptor status, final pathologic stage and genomic assays in the adjuvant setting.

Locally Advanced Breast Cancer

Locally advanced breast cancers are typically large and/or have extensive

regional lymph nodal involvement without evidence of distant metastatic disease at initial presentation. Approximately 10% to 20% of all patients with breast cancer have stage III disease with one-quarter of these patients initially inoperable at the time of diagnosis (See Figures 2.1 to 2.4).

Many locally advanced breast cancers are discovered by self-examination or routine physical examination. Occasionally, a discrete mass may not be present and diffuse infiltration of the breast tissue is. Seventy-five percent of patients with stage III disease will have clinically palpable axillary or supraclavicular lymph nodes at the time of diagnosis. This clinical finding is confirmed on pathologic examination in 66% to 90% of patients. Of the patients with positive nodes, 50% will have more than four nodes involved. Metastatic work up should be performed in the setting of stage III disease as 20% of patients are found to have distant metastases at presentation and are often asymptomatic. Distant metastases are also the most frequent form of treatment failure and usually appear within 2 years of the initial diagnosis.

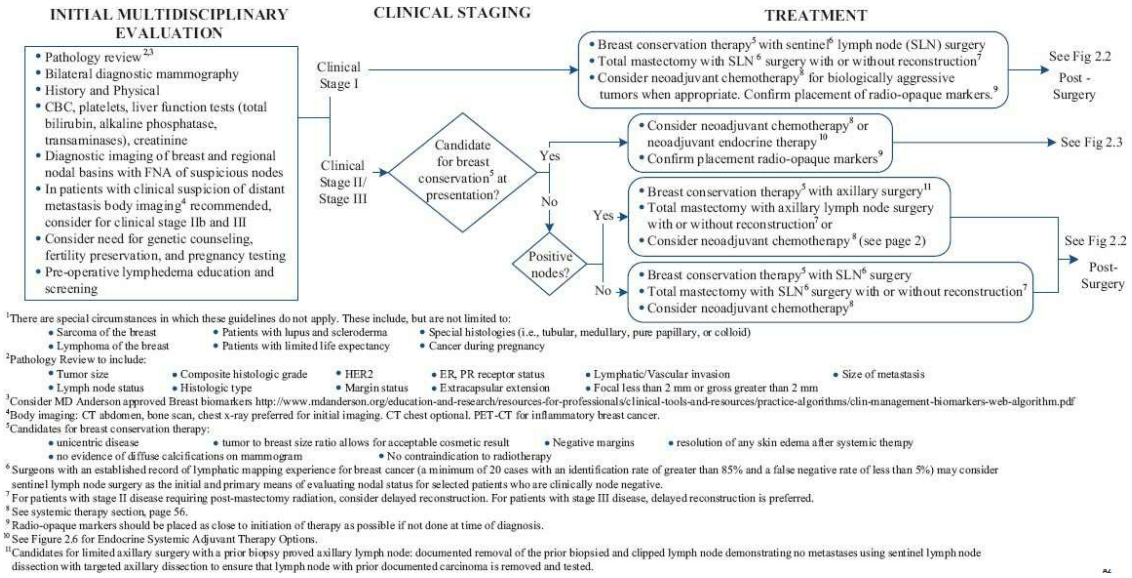
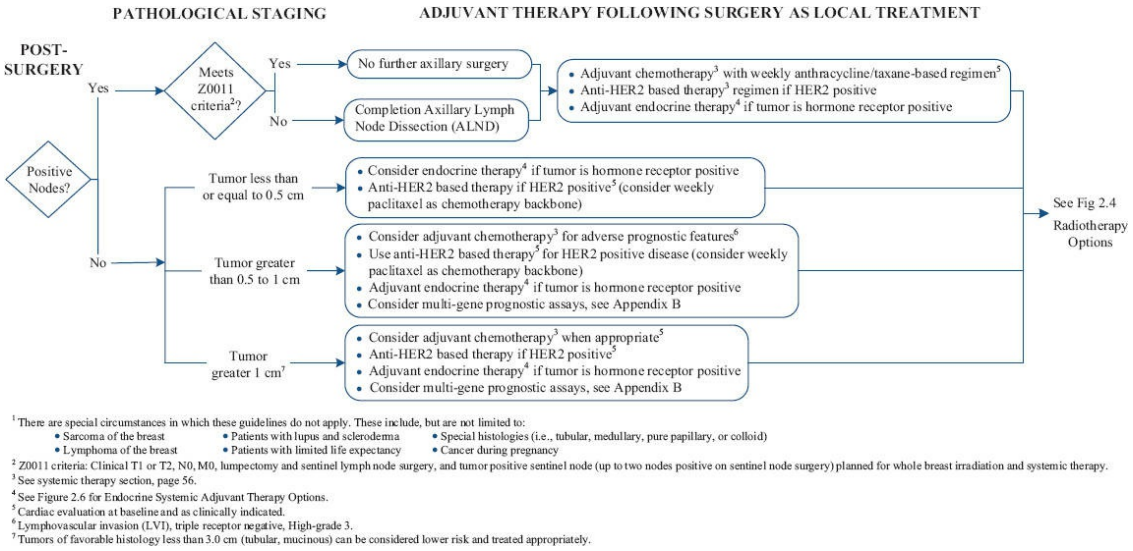
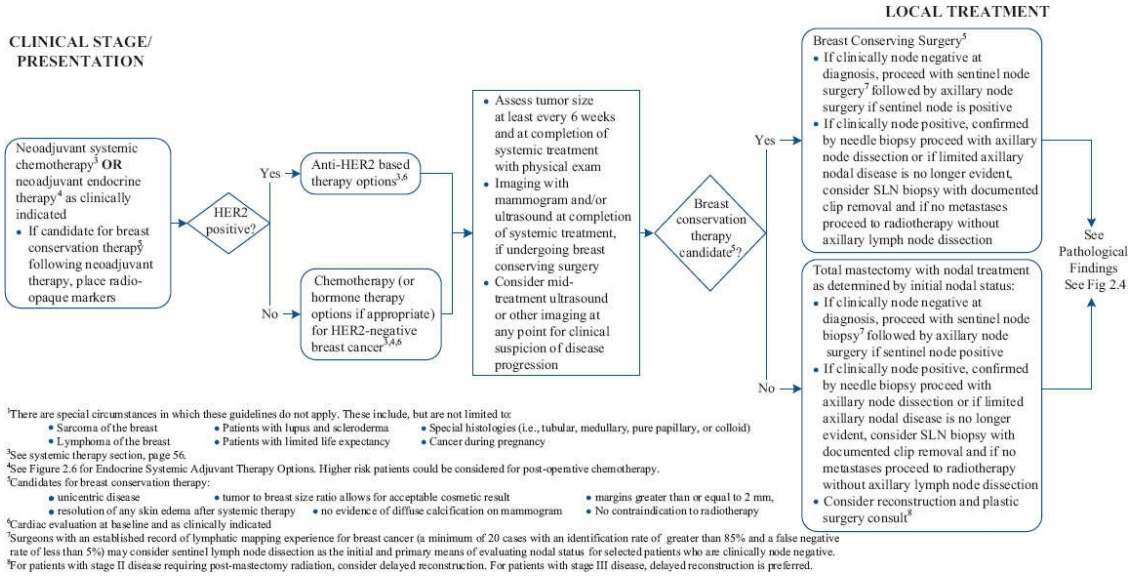


Figure 2.1 MDACC algorithm for stage I–III invasive breast cancer—initial treatment.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)



[1] There are special circumstances in which these guidelines do not apply. These include, but are not limited to:
• Sarcoma of the breast • Patients with lupus and scleroderma • Special histologies (i.e., tubular, medullary, pure papillary, or colloid)
• Lymphoma of the breast • Patients with limited life expectancy • Cancer during pregnancy
[2] Z0011 criteria: Clinical T1 or T2, N0, M0, lumpectomy and sentinel lymph node surgery, and tumor positive sentinel node (up to two nodes positive on sentinel node surgery) planned for whole breast irradiation and systemic therapy.
[3] See systemic therapy section, page 56.
[4] See Figure 2.6 for Endocrine Systemic Adjuvant Therapy Options.
[5] Cardiac evaluation at baseline and as clinically indicated.
[6] Lymphovascular invasion (LVI), triple receptor negative, High-grade 3.
[7] Tumors of favorable histology less than 3.0 cm (tubular, mucinous) can be considered lower risk and treated appropriately.

Figure 2.2 MDACC algorithm for stage I–III invasive breast cancer—post surgery.[2] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)



[1] There are special circumstances in which these guidelines do not apply. These include, but are not limited to:
• Sarcoma of the breast • Patients with lupus and scleroderma • Special histologies (i.e., tubular, medullary, pure papillary, or colloid)
• Lymphoma of the breast • Patients with limited life expectancy • Cancer during pregnancy
[3] See systemic therapy section, page 56.
[4] See Figure 2.6 for Endocrine Systemic Adjuvant Therapy Options. Higher risk patients could be considered for post-operative chemotherapy.
[5] Candidates for breast conservation therapy:
• unicentric disease • tumor to breast size ratio allows for acceptable cosmetic result • margins greater than or equal to 2 mm,
• resolution of any skin edema after systemic therapy • no evidence of diffuse calcification on mammogram • No contraindication to radiotherapy
[6] Cardiac evaluation at baseline and as clinically indicated
[7] Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of greater than 85% and a false negative rate of less than 5%) may consider sentinel lymph node dissection as the initial and primary means of evaluating nodal status for selected patients who are clinically node negative.
[8] For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is preferred.

Figure 2.3 MDACC algorithm for stage I–III invasive breast cancer—treatment.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

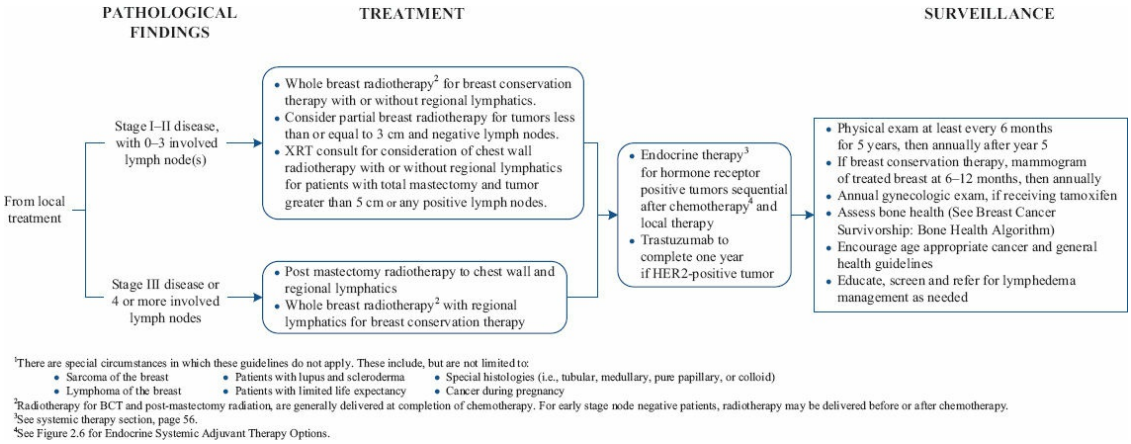


Figure 2.4 MDACC algorithm for stage I–III invasive breast cancer—treatment and surveillance.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

The standard of care in patients with locally advanced breast cancer is a neoadjuvant systemic therapy approach followed by surgery and adjuvant radiation therapy. If postoperative chemotherapy is planned, it should precede radiation therapy to avoid interrupting the treatment of systemic disease given distant metastasis is the most frequent form of treatment failure. Adjuvant hormonal therapy is routinely offered to all patients with hormone receptor-positive tumors.

Surgical options include breast conservation and mastectomy. If contralateral mastectomy is desired or planned a delayed or staged approach should be considered as the majority of risk is determined by the index malignancy. Axillary dissection is the standard for surgical management of the axilla however, the clinical landscape is changing in the setting of node-positive disease after neoadjuvant chemotherapy. In selected cases with limited nodal involvement and demonstration of clinical response, sentinel node dissection or targeted axillary dissection for axillary staging may be appropriate.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC), denoted within the AJCC staging system as T4d disease, is a rare, aggressive form of locally advanced breast cancer. It represents 1% to 6% of all breast cancers and presents as rapid onset of erythema, warmth, and edema of the breast. Onset of symptoms within 3 months is required to make the diagnosis of IBC, and distinguishes it from locally advanced breast cancer with secondary lymphatic invasion (T4b disease), which usually progresses slowly over

more than 3 months. Distinct from the majority of breast cancers, pain is also present in half of patients with IBC. Initial diagnosis of these physical findings as sequelae of an infectious process often delays diagnosis and treatment. The characteristic pathologic finding is dermal lymphatic invasion by carcinoma on skin punch biopsy. Ultimately, the diagnosis of IBC is based on the clinical evaluation, which includes the time frame for which the signs and symptoms appear and the absence of dermal lymphatic invasion pathologically does not exclude the diagnosis (See Figure 2.5).

Inflammatory breast carcinoma, similar to other forms of locally advanced breast cancer, is a systemic disease. Systemic staging evaluating for distant metastatic disease is indicated even in asymptomatic patients presenting with IBC. In a study of inflammatory carcinoma, local therapy as the only treatment modality resulted in poor outcomes; the median survival was less than 2 years, and the 5-year OS rate was 5%. The use of multimodality therapy in these patients has improved local control and overall survival over local therapy alone. Standard-of-care treatment is neoadjuvant chemotherapy with targeted therapy in the setting of HER2-positive disease, followed by modified radical mastectomy and adjuvant radiation therapy. With the addition of chemotherapy to the treatment regimen, the 5-year overall survival rate is 40%, although this number has not improved since the 1970s. Patients with disease progression during chemotherapy can proceed to preoperative radiation therapy or, in the setting of operable disease, surgery with modified radical mastectomy. BCT and sentinel lymph node dissection are not appropriate in these patients as dermal involvement extends beyond the tumor and precludes reliable drainage of tracer or dye to the lymph node basins. Breast reconstruction should be delayed, as nearly all patients will require chest wall and regional nodal radiation, to include axillary, periclavicular, and internal mammary nodes.

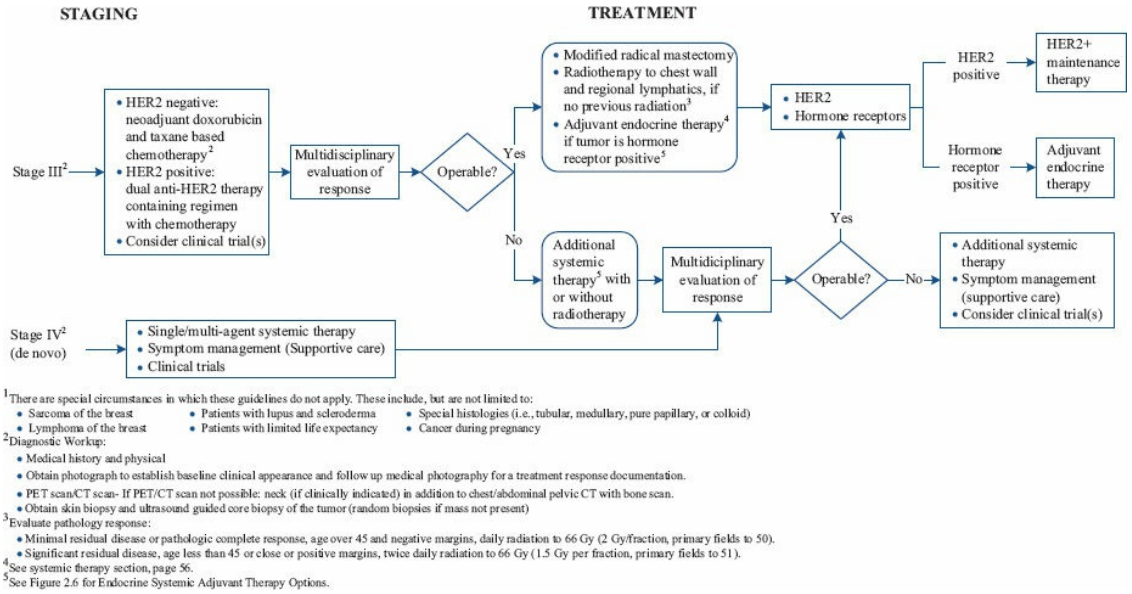


Figure 2.5 MDACC algorithm for inflammatory invasive breast cancer.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

Multidisciplinary Evaluation

Once the diagnosis of breast cancer has been made, the optimization of treatment decisions is best coordinated in a multidisciplinary fashion. The collaborative efforts of surgical oncologists with medical oncology, radiation oncology, geneticists, plastic and reconstructive surgeons, and cancer care coordinators can direct the choice of surgery, systemic therapy, radiation options, and reconstructive choices. The treatment algorithms depicted in Figures 2.1-2.5 represent the most current algorithms at the time of manuscript submission. Updated MD Anderson breast cancer treatment algorithms are available at https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-practice-algorithms/cancer-treatment-algorithms.html.

Local/Regional Therapy

Surgery

Management of the Breast Primary. Surgical management of the breast primary has evolved over time from the Halsted radical mastectomy which included resection of the breast, axillary nodes and pectoralis muscle. This evolution has been influenced by several landmark randomized, prospective clinical trials which have changed clinical practice as well as an understanding of the biology of breast cancer. In the

United States the majority of these were performed by the NSABP. A summary of selected trials are presented in Table 2.6.

Breast Conserving Therapy. Many patients with early-stage breast cancer can be treated effectively with BCT, which entails complete removal of the tumor with negative margins in combination with adjuvant radiation therapy. Six prospective randomized trials comparing breast conservation with radical or modified radical mastectomy have shown no survival advantage to mastectomy.

In the United States the trial establishing survival equivalence of breast conservation with mastectomy was the NSABP B-06. This trial included women with primary tumors up to 4 cm and clinical N0 or N1 nodal status. Patients were randomly assigned to modified radical mastectomy, lumpectomy with axillary lymph node dissection (ALND), or lumpectomy with ALND and radiation therapy. Histologically, negative margins were required in the breast conservation groups. Disease-free and overall survival rates did not differ significantly among the three groups, but the local recurrence rate was markedly reduced at 10 years by radiation therapy in the breast conserving groups such that 12% recurred after radiation therapy versus 53% with lumpectomy alone. These results supported breast conservation as an appropriate treatment strategy for patients with clinical stage I or II breast cancer and cemented radiation therapy as an integral part of BCT.

No significant differences in local control, disease-free survival, or overall survival have been observed, even after 20 year of follow-up, indicating that survival in these patients is not dependent on the choice of mastectomy versus BCT.

Given the oncologic equivalence with respect to outcome, the decision for BCT should include the patient's motivation and commitment to conservation of the natural breast. Inappropriate candidates for BCT include patients who are unable to receive radiation, diffuse disease, or persistent positive margins. Also relative contraindications include patients with small breast volume or high tumor to breast ratio, where the cosmetic result may be unacceptable following BCT. Increasingly, coordination with a plastic surgeon for oncoplastic reconstruction in conjunction with contralateral surgery for symmetry can yield excellent oncologic results without aesthetic compromise. Patients with large tumors may benefit from neoadjuvant systemic therapy to downstage the breast primary

thereby facilitating breast conservation. Although the use of BCT has increased during the past 14 years, nonclinical factors including socioeconomic demographics, insurance, and travel distance to the treatment facility persist as key barriers to BCT. Other factors that must be considered in making the choice between mastectomy and breast conservation surgery, are outlined in Table 2.7.

TABLE 2.6 Summary of Selected NSABP Therapeutic Trials for Invasive Breast Cancer

Trial	Treatment	Outcome
NSABP B-04	Total mastectomy vs. total mastectomy with XRT vs. radical mastectomy	No significant difference in disease-free or overall survival rates
NSABP B-06	Total mastectomy vs. lumpectomy vs. lumpectomy with XRT	No significant difference in disease-free or overall survival rates; addition of XRT to lumpectomy reduced local recurrence rate from 39% to 10%
NSABP B-13	Surgery alone vs. surgery plus adjuvant chemotherapy in node-negative patients with estrogen receptor-negative tumors	Improved disease-free survival rate for adjuvant chemotherapy group
NSABP B-14	Surgery alone vs. surgery plus adjuvant tamoxifen in node-negative patients with estrogen receptor-positive tumors	Improved disease-free survival rate for adjuvant tamoxifen group
NSABP B-18	Neoadjuvant chemotherapy with doxorubicin, cyclophosphamide, or both for 4 cycles vs. the same regimen given postoperatively	No significant difference in overall survival or disease-free survival rates (53–70% at 9 years in the postoperative group and 69% and 55% in the preoperative group)

NSABP B-21	Lumpectomy plus tamoxifen vs. lumpectomy plus tamoxifen plus XRT vs. lumpectomy plus XRT for node-negative tumors <1 cm	Combination of XRT and tamoxifen was more effective than either alone in reducing ipsilateral breast tumor recurrence
NSABP B-27	Neoadjuvant chemotherapy comparing AC × 4 cycles than surgery vs. AC × 4 cycles, docetaxel × 4 cycles than surgery vs. surgery between 4 cycles of AC and 4 cycles of docetaxel	Groups I and III were combined and compared with group II; clinical and pathologic complete response rates increased significantly among patients who received preoperative AC and docetaxel
NSABP B-32	SLN biopsy followed by axillary dissection vs. SLN biopsy alone for clinically node-negative patients	SLN identification rate was similar in both groups, accuracy was high for both, negative predictive value was high for both

NSABP, National Surgical Adjuvant Breast and Bowel Project; XRT, radiation therapy; AC, doxorubicin (Adriamycin), cyclophosphamide; SLN, sentinel lymph node.

Margin assessment is critical in BCT. Positive margins require reexcision or conversion to mastectomy. Determination of an appropriate negative margin has been controversial with national reexcision rates of 20% to 40%. Given this, the SSO in collaboration with the American Society for Radiation Oncology (ASTRO) developed national guidelines to address this clinical concern. These guidelines have defined a negative margin to be “no ink on tumor” and noted that wider margins did not significantly lower the risk of ipsilateral breast tumor recurrence. Furthermore, cases should be reviewed in a multidisciplinary fashion with consideration for reexcision in selected cases including extensive involvement by DCIS, discrepancy with clinical and radiographic tumor size and multiple close margins.

TABLE 2.7 Absolute and Relative Contraindications to Breast Conserving Therapy

Absolute Contraindications

Widespread disease that cannot achieve negative margins with a satisfactory cosmetic result

Radiotherapy use during pregnancy

Diffuse suspicious or malignant-appearing microcalcifications

Diffuse positive margins or positive margins after multiple excisions

Relative Contraindications

Active connective tissue disease involving the skin (especially scleroderma and lupus)

Large tumor to breast ratio

Prior radiation therapy to the chest wall or breast; knowledge of doses and volumes prescribed is essential

Women with a known or suspected genetic predisposition to breast cancer, who may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer. Prophylactic bilateral mastectomy for risk reduction may be considered.

Adapted from NCCN Guidelines. v2. 2016. *Invasive breast cancer.* https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

The standard for BCT at MDACC is excision of the tumor with negative margins followed by radiation therapy. An oncoplastic approach with reconstruction of the segmental defect is favored in the majority of cases. This is further discussed in the chapter on reconstructive surgery. An extensive intraoperative assessment of margins is standard practice. This includes a multidisciplinary effort by radiology, pathology, and surgery. The specimen is oriented by the surgeon and taken to the pathology suite where a specimen radiograph is performed to confirm excision of the lesion. The specimen is then inked and sectioned followed by an additional radiographic assessment to determine any close or involved margins. The specimen is also evaluated grossly for margins. Frozen section or additional margin excision is performed based on this assessment. Typically, surgical clips are placed within the segmental cavity to delineate the tumor bed and guide radiation treatment. In the adjuvant setting, radiation planning is initiated approximately 3 to 4 weeks after surgery. A dose of 50 Gy is given to the whole breast, and then 10 Gy is given to the operative site as a boost using tangential ports and computerized dosimetry in selected patients. Long-term mammographic surveillance of the preserved breast is necessary to detect potential in-breast recurrence.

The local recurrence rates following BCT, as documented in the Milan study, NSABP B-06, and the Danish Breast Cancer Cooperative Group study range from 2.6% to 18%, which is slightly higher than the range quoted for mastectomy (2.3% to 13%). However, there was no significant

difference in overall survival between BCT and mastectomy in any of these studies. Furthermore this data does not account for the major advancements in diagnosis, risk assessment, adjuvant hormonal therapy, chemotherapy, or targeted therapy. The ultimate goal of BCT for patients with early-stage breast cancer is to provide an optimal cosmetic result without compromising local control. Clearly, a multidisciplinary effort coupled with careful patient selection is critical for the successful outcome of BCT.

Mastectomy. The mastectomy has evolved greatly over time since the Halsted radical mastectomy, which included resection of the breast glandular tissue (including skin, nipple, and areola), pectoralis major and minor muscles and regional axillary nodes. The NSABP B-04 trial demonstrated equivalence of the modified radical mastectomy preserving the pectoralis muscle as compared to the radical mastectomy. With the advent of the sentinel lymph node technique allowing more precise axillary nodal evaluation, not all patients will require axillary dissection. The simple or total mastectomy removes the breast tissue with the majority of overlying skin, nipple, and areola, but preserves the majority of the axillary nodal contents and pectoralis muscles.

In 1991, popularization of the skin-sparing mastectomy (SSM) transformed breast oncologic surgery allowing for immediate breast reconstruction. SSM consists of a total mastectomy with resection of the nipple–areola complex, while allowing access to the axilla as indicated. It preserves a significant amount of the native skin envelope along with the inframammary fold, thus enhancing the aesthetic results of immediate breast reconstruction. Several retrospective reviews have documented the oncologic safety of this procedure, and in early-stage breast cancer the added benefit of immediate reconstruction can reduce the psychological impact of the surgery and improve body image without compromise of local, regional, or systemic recurrence rates when compared to conventional mastectomy.

Nipple-sparing mastectomy (NSM), which allows for preservation of the nipple and areolar complex is accepted as an oncologically safe procedure when there is no evidence of nipple involvement. Conventional indications for NSM include women with early-stage tumors located more than 2 cm from the nipple with a clinically negative axilla. For aesthetic reasons, very large or ptotic breasts are relative contraindications.

Particular care must be taken in women with central DCIS as preoperative imaging can underestimate the extent of disease; therefore careful attention to the final pathology is imperative in all cases. NSM is increasingly being performed for risk reduction in BRCA and other high-risk patients undergoing prophylactic mastectomy, with excellent oncologic and aesthetic results. In a recent multicenter Italian trial of 1,006 procedures, NSM failure rate, with NAC removal for any reason was 11.5%, with a NAC necrosis rate of 4.8%, and large skin-flap necrosis occurring in 2.3%. All NSM must be performed in close consultation with a plastic surgeon and patient selection and surgeon comfort remain important considerations.

Prophylactic mastectomy is utilized in high-risk patients as a risk-reduction strategy resulting in 90% to 95% relative risk reduction. Among average risk women, rates of contralateral prophylactic mastectomy (CPM) in the United States have increased dramatically over the past 10 years. This is in contrast to declining rates of contralateral breast cancer (CBC) particularly in patients with ER-positive breast cancer. Furthermore, the risk of a CBC in women with sporadic breast cancer is low and estimated at 0.5% to 0.75% per year among women with early-stage disease. Several studies have not shown a survival advantage to CPM, even among the highest risk individuals. When discussing CPM, it is important to note the absolute benefit in risk reduction may be modest in addition to comparing the risk of systemic recurrence and death from the index malignancy and medical comorbidities against the risk of a future contralateral breast cancer.

Management of the Axilla

Axillary staging is performed in all patients with invasive breast cancer, as identifying patients with nodal metastases impacts prognosis and multidisciplinary local, regional, and systemic treatment recommendations. Axillary surgery for breast cancer is one of the most rapidly evolving areas in breast cancer treatment.

Clinically Node Negative Disease. ALND was once considered the gold standard for evaluating the draining nodal basin for lymph node metastases. However, lymphatic mapping with sentinel lymph node (SLN) dissection is now the standard of care for axillary staging in clinically node negative patients with breast cancer. The SLN is defined as the first lymph

node or group of nodes that receive lymphatic drainage from a primary breast cancer and as such are most likely to contain metastatic disease. Several randomized clinical trials have demonstrated the feasibility and oncologic safety of SLN dissection including the NSABP B-32 clinical trial. Most studies report successful SLN detection in 94% to 98% of patients, an accuracy rate of 97% to 100%, and a false-negative rate of 0% to 15%. Furthermore, it is well documented that SLN dissection results in reduced morbidity including pain, paresthesia, decreased range of motion, seroma, and lymphedema.

At MDACC, lymphatic mapping is performed with preoperative or intraoperative injection of Technetium-99 followed by transcutaneous localization of increased radioactivity performed with a handheld gamma probe, with or without the addition of isosulfan blue dye. Use of dual tracer has been shown to decrease false-negative rates and should strongly be considered, particularly in patients who may have impaired lymphatic drainage to the axilla, such as in cases of prior breast and/or axillary surgery or radiation. Preoperative lymphoscintigraphy, although not mandatory, can also be used to identify the SLN and document patterns of lymphatic drainage. Once the SLN(s) are removed, the axilla is examined to confirm a drop in radioactivity to less than 10% of the highest lymph node count identified. A residual high level of radioactivity indicates that additional sentinel nodes remain in the nodal basin.

Studies have shown that approximately 24% of patients with early-stage clinically node-negative breast cancer will have a positive sentinel node. The incidence of finding a positive SLN correlates with primary tumor size.

Management of SLN Positive Patients. Traditionally, ALND was performed in the setting of a positive SLN. A paradigm shift occurred in 2010 following results of the ACOSOG Z0011 trial which challenged the traditional approach. This trial definitively changed the management of SLN positive axillary metastases in patients with early-stage clinically node-negative breast cancer.

The Z0011 trial enrolled patients with clinically node-negative, T1 or T2 early-stage breast cancer undergoing BCT and SLN dissection, with three or fewer positive SLNs as detected by hematoxylin and eosin (H&E) staining. Critically important to this study was the requirement that all patients received postoperative whole breast radiation and chemotherapy

as indicated. Patients were randomized to completion axillary dissection versus no further axillary surgery. At a median follow-up of 6.3 years, there was no difference in overall survival (ALND 91.9% vs. 92.5% in SLN-only; $P = 0.24$) or disease free survival (ALND 82.2% vs. 83.8% in SLN-only; $P = 0.13$) at 5 years. There was no significant difference in local recurrence reported (3.6% of the ALND group versus 1.8% of the SLND-only group). After ALND alone, ipsilateral axillary recurrence was identified in 0.5% of patients versus 0.9% in the SLN dissection-only arm. Although this study closed early due to poor accrual, results suggest that in clinically node-negative patients with early-stage breast cancer who will receive whole breast radiotherapy and systemic adjuvant therapy as indicated, ALND does not confer an improved survival advantage. In this setting SLN dissection alone for appropriate staging with completed adjuvant therapy may offer excellent regional control with decreased morbidity.

Since the publication of these practice-changing results, the Z0011 findings have been rapidly and widely adopted and are now considered standard practice. It is important to note that these findings are not applicable to all patients including those with locally advanced (T3 or T4) disease, those who received neoadjuvant chemotherapy or those undergoing mastectomy.

Clinically Node-Positive Disease. In the setting of clinical nodal involvement at presentation, axillary dissection is the standard of care. This is evolving in the setting of neoadjuvant chemotherapy in selected patients where axillary staging may be appropriate.

ALND consists of en bloc removal of the level I and II axillary nodal tissue. When level III nodes are grossly or pathologically involved, removal of these nodes may be indicated, however, removal of clinically negative level III lymph nodes is of little benefit with respect to staging because only 1% to 3% of stage I or II patients show level III involvement in the absence of level I or level II disease. Level III dissections carry a substantially higher risk of subsequent lymphedema, particularly when used in conjunction with radiation therapy. ALND should preserve the long thoracic and thoracodorsal nerves and avoid stripping of the axillary vein. A closed-suction drain is typically placed and removed once the drainage has sufficiently decreased.

Management of Clinical N1 Disease After Neoadjuvant

Chemotherapy. Following neoadjuvant chemotherapy, pathologic complete response (pCR) in the axillary nodes is found in 40% of patients presenting with biopsy proven node-positive disease. This observation led to several clinical trials including ACOSOG Z1071, SENTINA (Arm C) and SN FNAC, evaluating the feasibility and accuracy of SLN dissection as axillary staging after neoadjuvant chemotherapy in clinical N1 disease. Although the false-negative rate of SLN in this setting was above the predetermined threshold, several important factors associated with and impacting the false negative rate were described. This included use of dual agent mapping technique, evaluation of at least 2 to 3 SLNs, IHC evaluation in addition to H&E staining and excision of the clipped (biopsy proven) node.

The results of these findings led to refined technique termed targeted axillary dissection (TAD). This procedure involves SLN dissection and selective targeted excision of the clipped (biopsy proven) axillary node. At MDACC, at the time of initial evaluation, patients undergo an axillary ultrasound with biopsy of any suspicious nodes. In the setting of N1 disease a clip is placed to mark the biopsy proven axillary node. Patients with advanced nodal involvement by ultrasound or examination (matted nodes, internal mammary, infraclavicular, or supraclavicular nodes) are not candidates for this approach and will undergo axillary dissection. Response is documented during chemotherapy with ultrasound and clinical exam. In selected patients planned for TAD, the clipped node is preoperatively localized with an I-125 radioactive seed or wire. Intraoperatively, dual lymphatic mapping for SLN identification is employed and targeted excision of the clipped node is performed. Excision is confirmed with specimen radiograph. In approximately 23% of cases the clipped node will not be a sentinel node. Compared with ALND, the false-negative rate of this approach was 10.1% with sentinel node biopsy alone, 4.2% for excision of the clipped node alone and 2.0% for TAD. In carefully selected patients TAD alone may offer an accurate approach to axillary staging and assessment of residual disease with limited morbidity.

Radiation Therapy. The role of radiation therapy in breast cancer has been well established as an adjunct to surgery in the management of local regional recurrence. In early-stage breast cancer, BCT with whole-breast radiation has been associated with equivalent long-term survival results versus mastectomy alone; recurrence rates are improved in all subsets of

patients and radiation therapy to the nodal basin helps achieve long-term regional control.

The addition of a radiation boost to the primary tumor site after whole-breast radiation to reduce the risk of local recurrence has been validated in two prospective randomized trials. In the European Organization for Research and Treatment of Cancer (EORTC) 10981–22023 trial, patients were randomly assigned to receive whole-breast irradiation of 50 Gy plus a boost dose of 16 Gy compared with no boost in patients with negative surgical margins. The 10-year rate of local recurrence was reduced from 10.2% without a boost to 6.2% with a boost ($P < 0.0001$), with a hazard ratio of 0.59 in favor of a boost; the benefit in reducing local recurrence was maintained through 16 years of follow-up.

For tumor recurrence with BCT, the majority of relapses occur at or near the original tumor bed, rarely extending beyond 1 to 2 cm of the prior cavity. This has led to the rationale that accelerated partial breast irradiation (APBI) could be used to deliver a homogenous dose of radiation within a confined space. Advantages of APBI include shorter treatment (5 days vs. 6 weeks), less scatter radiation to the lungs, heart, and coronary vessels, and less skin burning and desquamation. Preliminary studies of APBI suggest that rates of local control in highly selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, follow-up is limited and studies are ongoing; compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Currently, the consensus statement from ASTRO, states that possible candidates for APBI include women older than 60 years with unifocal T1 N0 M0 ER-positive breast cancer, who are not BRCA 1/BRCA 2 mutation carriers, and who have infiltrating ductal or a favorable ductal subtype, with negative margins not associated with an extensive intraductal component or LCIS.

Postmastectomy radiation therapy (PMRT) may reduce the risk of local–regional failure. Traditionally, the greatest benefit of PMRT is seen in patients at highest risk for local regional failure with greater than four positive lymph nodes, tumor size greater than or equal to 5 cm, T4 disease, or positive margins. Other factors associated with local regional failure include age, histologic grade of tumors, presence of lymphovascular invasion, and extracapsular spread of the lymph nodes. There has been considerable debate whether patients with one to three positive axillary

lymph nodes benefit from PMRT. There seems to be more data suggesting better outcomes with this subset population who undergo PMRT, but it has been unclear whether it is the effect of PMRT itself, or the improved delivery and efficacy of systemic therapy or better surgical technique that contribute to these results. Little prospective data exists on present-day local–regional recurrence (LRR) rates after mastectomy without PMRT. Sharma et al. examined women with early-stage breast cancer and one to three positive axillary lymph nodes treated with mastectomy showing that the 10-year risk of LRR was not significantly different between patients without lymph node metastases and patients with one positive lymph node. They concluded that in this era of improved systemic therapy, any potential absolute LRR reduction and survival advantage that may be gained from the use of PMRT must be balanced against possible morbidities associated with radiation.

Radiotherapy is also highly effective for treatment of axillary disease, with locoregional control rates comparable to axillary surgery. The AMAROS trial was a noninferiority trial enrolling patients with T1/T2 tumors without palpable axillary disease who were found to have positive SLN. Although the planned noninferiority test was underpowered due to a low overall event rate, at 6 years median follow-up, radiotherapy provided comparable regional control compared to ALND. Importantly, the rate of lymphedema at 1, 3, and 5 years was markedly lower in the radiotherapy arm.

Breast Reconstruction. For the majority of patients treated with mastectomy, breast reconstruction should be offered. Immediate reconstruction is contraindicated in the setting of inflammatory breast cancer. Breast reconstruction may involve autologous tissue, synthetic implants, or both. The options, patient selection, decision-making, and technical details of breast reconstruction including are discussed in chapter 25.

Although satisfactory results can be obtained with either immediate or delayed reconstruction, an important consideration is the likelihood of postmastectomy radiation (PMRT). Acute and chronic complications and poor aesthetic outcomes have been identified in patients who undergo immediate reconstruction with placement of a permanent breast implant followed by PMRT. For this reason, close multidisciplinary discussion with a radiation oncologist is important to ensure that optimal oncologic

delivery of radiation is not compromised by an underlying implant or tissue expander. In cases where receipt of PMRT is unknown or planned, a delayed immediate approach may be employed whereby the patient undergoes SSM with insertion of a saline-filled tissue expander. This serves as an adjustable scaffolding to preserve a three-dimensional contour of the breast skin envelope. Based on pathologic evaluation, if the patient requires PMRT, the tissue expander can be deflated to allow radiation delivery followed by delayed reconstruction typically with autologous tissue. If no PMRT is required, then the patient can undergo definitive reconstruction once the desired breast size and symmetry has been achieved.

Systemic Therapy

Chemotherapy

As our knowledge of the complexity of breast cancer grows, it is clear that breast cancer is no longer a single disease entity, but rather a group of molecularly distinct subtypes each with different prognosis, natural histories, and chemotherapeutic sensitivities. The decision to receive chemotherapy is becoming highly individualized and is based on a combination of hormone receptor status, HER2 amplifications, tumor grade, lymph node status, and Ki-67 proliferation index. Systemic treatment decisions should be made within a multidisciplinary setting. Typical regimens include anthracycline and taxane-based therapy with the addition of targeted therapy where indicated. Detailed discussion of specific chemotherapy regimens and current guidelines are available through the NCCN at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Adjuvant chemotherapy is directed at treating occult micrometastatic disease, thereby reducing the risk of local and systemic recurrence. Chemotherapy works most effectively when tumor volume is small and still in its linear growth phase. This rationale led to some of the first adjuvant clinical trials of polychemotherapy versus observation in lymph node–positive breast cancer that showed improved disease-free and overall survival with chemotherapy.

To assist in determination of the benefit of chemotherapy on recurrence and survival, a number of prognostic tests have been developed using gene expression profiling. Adjuvant! Online (www.adjuvantonline.com) is a widely used, freely available web-based tool. It considers multiple clinical

and pathologic factors and produces estimates for recurrence and mortality. In addition, this program incorporates the effect of comorbid conditions in the determination of prognosis and benefit from various therapeutic interventions. Adjuvant! Online has been independently validated by Canadian investigators showing concordance with actual recurrence and mortality rates within 1% of predictions based on this model.

The most widely used commercially available test in the United States is Oncotype DX (Genomic Health Inc, Redwood City, CA). This reverse-transcriptase polymerase chain reaction (RT-PCR) assay is intended for use in Hormone Receptor (HR) positive node-negative breast cancer patients who will receive 5 years of tamoxifen. It measures the gene expression of 16 cancer-related genes (including ER, PR, HER2, and Ki-67) in paraffin-embedded tumor tissue and uses a regression model to calculate a recurrence score (RS) that is an estimate of the risk of developing distant metastases at 10 years. Two suggested cut-off points categorize patients into low (RS < 18), intermediate (RS ≥ 18 < 31), and high (RS ≥ 31) risk groups corresponding to 6.8%, 14.3%, and 30.5% risk of distant recurrence at 10 years after 5 years of tamoxifen therapy, respectively. Similarly, these subgroups by RS also correlate with risk of local regional recurrence. Furthermore, analysis using the population studied in NSABP B20 (ER-positive, node negative) suggested the predictive power of this genomic assay in regards to the benefit of chemotherapy within this subset of patients such that in the high RS group chemotherapy in addition to tamoxifen resulted in increased survival whereas in the low RS group there was no survival advantage with chemotherapy over tamoxifen. The benefit in the intermediate RS group was less clear.

The TAILORx (Trial Assigning Individualized Options for Treatment) study was designed to answer the question regarding benefit of chemotherapy within the intermediate RS group. This trial randomized patients with HR-positive, node-negative breast cancer and an intermediate RS to chemotherapy and endocrine therapy versus endocrine therapy only. Patients with a score of 0 to 10 were assigned to receive endocrine therapy alone, and those with a score of 26 or higher were assigned to receive chemotherapy plus endocrine therapy. Patients with a midrange score of 11 to 25 were randomly assigned to receive chemotherapy plus endocrine therapy or endocrine therapy alone. To minimize the potential for under

treatment of the enrolled participants, investigators used lower thresholds for low-, intermediate-, and high-risk individuals from the originally defined scores. Currently, only results of the low-risk group have been reported including 1,626 women with a recurrence score of 0 to 10 assigned to receive endocrine therapy alone without chemotherapy. At 5 years, invasive disease-free survival (DFS) was 93.8%, distant recurrence-free survival was 99.3%, and overall survival was 98.0% in this group. Results for the intermediate group are eagerly awaited.

The FDA-approved 70-gene signature MammaPrint (Agendia) was developed at the Netherlands Cancer Institute from a retrospective series of 78 patients younger than 55 years who received no adjuvant systemic therapy and had T1/T2, node-negative breast cancer. This assay stratifies patients into low and high-risk groups with respect to development of distant metastasis. Recently, the results of the prospective multicenter randomized MINDACT (microarray in node-negative disease may avoid chemotherapy) trial were published evaluating the clinical utility of MammaPrint in selecting patients with node-negative, HR-positive breast cancer for adjuvant chemotherapy. These results showed that MammaPrint Low Risk patients had a 94.7% 5-year distant metastasis free survival without chemotherapy, even in the presence of high-risk clinical factors such as node positivity, high grade, large tumor size, and age <50 years. The absolute difference in 5-year survival rate was 1.5% lower in those receiving no chemotherapy, with no difference in distant metastasis in the subgroup of patients with ER-positive, HER2-negative, and either node-negative or node-positive disease. The authors suggest that the use of MammaPrint can therefore reduce overtreatment of patients in this group by 46%. These findings begin to validate changes in clinical practice and help avoid unnecessary treatment with chemotherapy in selected patients limiting long-term side effects of cardiac toxicity, secondary cancers, early menopause, and psychosocial harm.

Tumor Biology and Choice of Chemotherapy. Important differences in the clinical behavior of estrogen receptor (ER)-positive and negative breast cancers have long been recognized. Gene expression profiling studies have identified at least four distinct molecular subtypes of breast cancer: basal-like, HER2-enriched, luminal A, and luminal B. In addition to differing biologic and clinical behaviors they also have unique chemosensitivities. While gene expression profiling is not routinely

performed, immunohistochemical surrogates are commonly used to determine subtype. In general, the basal-like and HER2-positive subtypes are predominately ER-negative, while the luminal subtypes are ER-positive. Clinically, the triple negative phenotype is used to identify basal-like cancers, however, this misclassifies up to 30% of basal-like cancers.

Hormone Receptor-Positive Breast Cancer

Hormone receptor-positive breast cancer comprises about 75% of all invasive breast cancers. Substantial molecular differences exist between high- and low-risk ER-positive tumors. As previously discussed, Oncotype DX and MammaPrint have recently been validated as a means to avoid chemotherapy in favor of endocrine treatment alone in patients with low-risk scores. Luminal A cancers (Oncotype Dx "low RS," MammaPrint "low risk") are characterized by high expression of ER and ER-related genes, and have low expression of proliferative markers such as Ki-67 and are typically low grade. These patients have a good prognosis and high likelihood of benefit from endocrine therapy. In contrast, luminal B (Oncotype DX "high RS," MammaPrint "high risk") cancers are characterized by lower expression of ER and ER-related genes, and high expression of proliferation markers. These are typically high grade tumors and have a poorer prognosis. Standard chemotherapeutic regimens in addition to endocrine therapy should be considered for these patients.

HER2-Positive Breast Cancer

Between 20% and 25% of breast cancers are HER2-positive which is predictive of a response to anti-HER2 agents such as trastuzumab (Herceptin; Genentech, South San Francisco, CA) a humanized monoclonal antibody that targets the extracellular domain of the HER2 receptor. In the preoperative setting, pathologic complete response rates of up to 65% have been reported with trastuzumab in combination with chemotherapy. The administration of chemotherapy in combination with 1 year of trastuzumab is associated with a 50% reduction in the risk of recurrence and about a 30% reduction in the risk of death. This has been confirmed in a recent Cochrane meta-analysis of randomized controlled trials (RCTs), including six adjuvant and two neoadjuvant studies (NSABP B-31, NCCTG N9831, BCIRG 006, HERA, FinHer, PACS-04, Buzdar and NOAH), and 1 year of adjuvant trastuzumab has become standard of care in HER2-positive breast cancers.

Pertuzumab (Perjeta, Genentech, South San Francisco, CA) is an FDA-approved treatment for HER2-positive metastatic breast cancer. It is a HER2 dimerization inhibitor used in combination with Herceptin (trastuzumab) and docetaxel as first-line treatment. The CLEOPATRA trial published in 2012 in the New England Journal of Medicine studied the safety and efficacy of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel. Median progression free survival was 18.5 months versus 12.4 months in the pertuzumab groups and control groups respectively. At ASCO 2017, an abstract on the APHINITY trial was presented. This randomized trial evaluated 4,805 women with early breast cancer assigned to receive standard adjuvant chemotherapy for 18 weeks plus 1 year of either trastuzumab and placebo or trastuzumab and pertuzumab in the adjuvant setting. Modest benefits were seen in the group receiving pertuzumab with trastuzumab versus the placebo/trastuzumab group with respect to the development of invasive breast cancer (7.1% vs. 8.7% at median follow-up of almost 4 years). At 3 years, 94.1% of patients who received pertuzumab were seen to be free of invasive breast cancer versus 93.2% of patents in the placebo group. Slightly greater benefits were seen with the use of pertuzumab in patients with node-positive disease.

Triple Negative Breast Cancer

Triple negative cancers are highly proliferative and carry a worse prognosis than other breast cancer subtypes but are uniquely sensitive to standard chemotherapy. Currently, DNA-damaging agents are being tested in this subgroup in order to exploit the strong association between these tumors and the presence of BRCA1 mutations. Homologous recombination, a high-fidelity DNA repair pathway, relies on functioning BRCA1. When this pathway is dysfunctional the poly (ADP-ribose) polymerase (PARP) DNA repair mechanisms take over. PARP has been identified as an important drug target in order to bring about so-called “synthetic lethality” of BRCA mutated tumors. PARP-inhibitors have been investigated in phase II studies for triple negative and BRCA1/2-deficient cancers and results to date are promising. Epothilones, antiangiogenic agents, EGFR inhibitors, mTOR inhibitors, PI3 kinase inhibitors, and agents that induce DNA double-strand breaks such as platinum agents are to be tested in clinical trials.

Furthermore, six molecular subtypes of triple negative breast cancer

have been described—basal-like 1, basal-like 2, mesenchymal-like, mesenchymal stem-like, immunomodulatory, and luminal AR. This may explain the heterogeneous nature of this subtype in response to conventional chemotherapy and identify opportunities for targeted therapy.

Endocrine Therapy

Endocrine therapy has been associated with significant reductions in the risk of local recurrence, distant metastasis, and contralateral breast cancer. Tamoxifen, which was originally recommended for the treatment of postmenopausal women with ER-positive breast cancer, is now indicated for a much broader range of patients. Tamoxifen therapy is considered standard of care for premenopausal women with tumors expressing ER or PR hormone receptors, regardless of age or nodal status. Tamoxifen therapy is generally well tolerated with treatment-limiting adverse effects in less than 5% of patients. In addition to its antitumor properties, tamoxifen increases bone density and reduces serum cholesterol levels. However, tamoxifen also increases the incidence of endometrial cancer and thromboembolic events. Standard treatment with tamoxifen is 5 years based on data from NSABP B-14 indicating that 10 years of tamoxifen use offer no survival advantage over 5 years, however, there is ongoing research in this area and NCCN guidelines now recommend consideration of 5 to 10 years of endocrine therapy.

In 2014, results of the long-awaited SOFT trial for premenopausal patients looked at 4,690 patients from two phase II trials comparing combined therapy with exemestane and ovarian suppression versus tamoxifen and ovarian suppression for 5 years. At a median follow-up of 67 months, DFS and rate of freedom from breast cancer at 5 years was not significantly different and side effect profiles were similar to those in postmenopausal women. However, pre-menopausal patients who received adjuvant chemotherapy due to increased risk, in the exemestane/ovarian suppression group, were found to have a significantly improved freedom from breast cancer at 5 years (85.7%). This led to the conclusion that adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence in premenopausal women with hormone-receptor–positive early breast cancer.

Current NCCN recommendations for postmenopausal women include aromatase inhibitors as a component of adjuvant endocrine therapy. The

aromatase inhibitors anastrozole, letrozole, and exemestane work by inhibiting aromatase, an enzyme that catalyzes the conversion of adrenal corticosteroids to estrogens and therefore decreases the conversion of precursor hormones to estrogen in adipose tissue. In the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial, the efficacy and side effect profiles of anastrozole and tamoxifen were compared in postmenopausal women. For postmenopausal patients with early-stage breast cancer, anastrozole resulted in a higher DFS rate (86.9% vs. 84.5%) than tamoxifen, longer time to recurrence, and lower incidence of contralateral breast cancer. The results also demonstrated that the incidence of endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flashes occurred significantly less frequently with anastrozole, whereas musculoskeletal disorders and fractures occurred less frequently with tamoxifen. As a result of the ATAC trial, anastrozole is now the preferred hormone therapy for postmenopausal patients with receptor-positive breast cancer. For patients who have already been taking tamoxifen, studies have shown that switching to an aromatase inhibitor is safe, and results in improvements in DFS rates in postmenopausal women.

Ovarian suppression with LHRH-agonists (e.g., luprolide, triptorelin or goserelin) or ovarian ablation is another effective adjuvant endocrine treatment in premenopausal women. ASCO now recommends that women with stage II or III breast cancers who are advised to receive adjuvant chemotherapy should receive ovarian suppression in combination with either tamoxifen or an aromatase inhibitor. Additionally, women with stage I or II breast cancers at higher risk of recurrence who are considered for chemotherapy may be offered ovarian suppression with endocrine therapy. Women with stage I breast cancers not warranting chemotherapy, such as those with node-negative cancers 1 cm or less, should not receive ovarian suppression (See Figure 2.6).

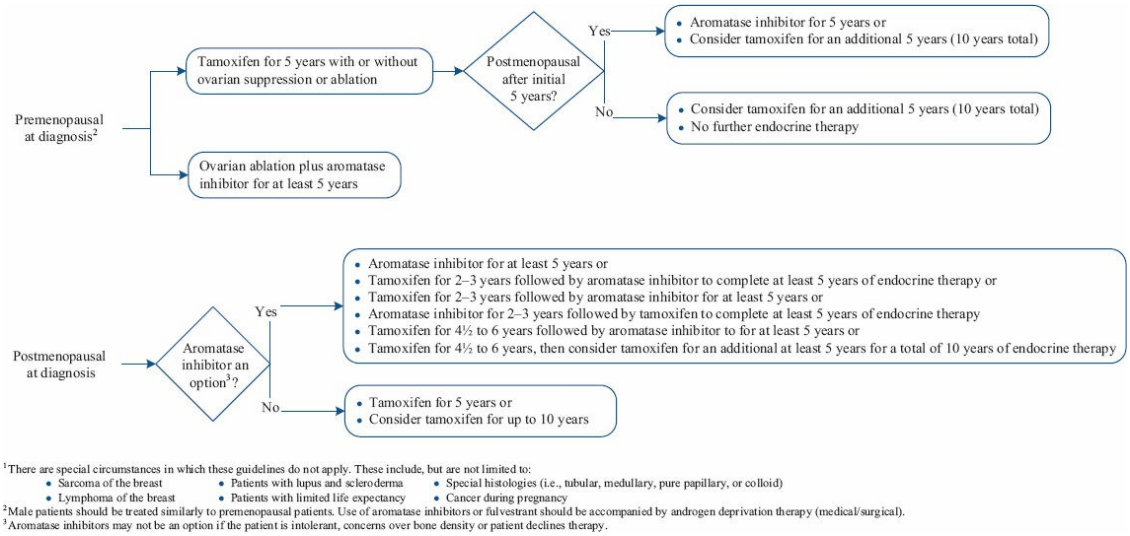


Figure 2.6 MDACC algorithm for endocrine systemic adjuvant therapy of invasive breast cancer.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

Neoadjuvant Systemic Therapy

Neoadjuvant Chemotherapy

Several phase II studies and eight randomized controlled trials have observed no difference in DFS or overall survival between adjuvant (chemotherapy following surgery) and neoadjuvant (chemotherapy preceding surgery) therapy. Adjuvant chemotherapy is equally effective up to 12 weeks after definitive surgery but may be compromised by delays of more than 12 weeks after definitive surgery.

These trials however, uncovered multiple benefits to neoadjuvant chemotherapy (NAC) including increased rates of BCT, conversion of tumors from inoperable to operable, and gaining prognostic information at an individual patient level based on response to therapy, which is particularly important in patients with triple negative and HER2-positive breast cancers. It also allows time for genetic testing, which can influence the operative plan in patients with high-risk mutations and can allow time for operative planning in patients electing for reconstruction after mastectomy.

Increasingly, NAC may allow for downstaging of disease in the axilla, providing an opportunity to modify systemic treatment if there is no or poor preoperative therapy response or progression of disease, and may allow for less radiotherapy if axillary nodal disease is cleared after receiving NAC. Finally, NAC provides an excellent research platform to test novel therapies, continue clinical trials, and test predictive biomarkers

for ongoing evolution in the treatment of breast cancer.

Possible disadvantages to NAC include possible overtreatment with systemic therapy if clinical stage is overestimated, possible undertreatment with radiotherapy if clinical stage is underestimated, and the possibility of disease progression during preoperative systemic therapy. For these reasons, treatment within a multidisciplinary conference with ongoing reassessment and communication among treatment teams is critical.

Candidates for NAC include those with inoperable breast cancer including inflammatory breast cancer, N2/N3 nodal disease, or T4 tumors as well as patients with operable breast cancer with a large primary tumor relative to breast size in a patient who desires breast conservation, as well as patients in whom adjuvant chemotherapy is planned (Triple negative, HER2 positive, node positive). Patients who are not appropriate for NAC include patients with extensive in situ disease in whom the extent of invasive carcinoma is not well defined or patients with a poorly delineated extent of tumor preoperatively, either by radiologic or physical exam. It is critical to note that definitive tissue diagnosis both of the primary tumor and nodal disease is required, with placement of radiologically confirmed localizing clips prior to the initiation of chemotherapy to ensure proper localization of the tumor during surgery in the event that the chemotherapy produces a complete clinical response.

Neoadjuvant Endocrine Therapy

Endocrine therapy in the neoadjuvant setting has been utilized in HR-positive breast cancer particularly in postmenopausal women. This is largely based on the significant impact on survival and recurrence outcome seen in the adjuvant setting. Although not associated with high rates of pCR, neoadjuvant endocrine therapy has been documented to facilitate increasing rates of breast conservation in this population. Furthermore, response to therapy may be followed by change in Ki-67 percentage or evaluation of the PEPI (preoperative endocrine prognostic index) score. Several trials have shown superior response to aromatase inhibitors as compared to tamoxifen in the neoadjuvant setting in postmenopausal women. Moreover, the ACOSOG Z1031 trial compared therapy with exemestane, letrozole and anastrozole in the preoperative setting is currently finding similar rates of BCT conversion among the therapies and similar biologic effect.

Surveillance

After primary therapy for invasive breast cancer, patients must be made aware of the long-term risk for recurrent or metastatic disease. Although most studies report that the majority of recurrences occur within 5 years after primary therapy, recurrences can occur more than 20 years after primary therapy.

The published American Society of Clinical Oncology (ASCO) guidelines for follow-up recommend scheduled visits that include a detailed cancer-related history and physical examination every 3 to 6 months for years 1 through 3, every 6 to 12 months for years 4 through 5, and every 12 months thereafter. Mammography is done 6 months after the completion of BCT to allow surgery- and radiation-induced changes to stabilize, and then yearly. For patients who have undergone mastectomy, a contralateral mammogram is obtained yearly. Clinicians should counsel patients to adhere to adjuvant endocrine therapy. Routine bone scans, skeletal surveys, laboratory tests, and computed tomographic scans yield an extremely low rate of occult metastases in otherwise asymptomatic patients and are not cost effective for patients with early-stage breast cancer.

Locally Recurrent Breast Cancer

The time course, clinical significance, and prognosis of locally recurrent breast cancer vary between patients undergoing BCT and those undergoing mastectomy. Local recurrence rates of 5% to 10% at 8 to 10 years have been reported for patients after breast conservation. Local recurrence typically occurs over a protracted time and is associated with systemic metastases in less than 10% of patients. By contrast, local chest wall recurrence following mastectomy typically occurs within the first 2 to 3 years after surgery, and may occur more than 10 years later; it is associated with distant metastases in as many as two-thirds of patients (See Figure 2.7).

Any patient with a local recurrence should undergo complete restaging after detection of the recurrence. Initial work up should also include bilateral diagnostic mammogram for patients with an intact breast, ultrasound evaluation of affected breast and nodal basins, core-needle biopsy with assessment of hormone receptor and HER2-neu status, and consideration of neoadjuvant chemotherapy. For patients with a purely

local recurrence, surgical excision plus radiation therapy provides better local control than does either modality alone. In patients with isolated in-breast tumor recurrence, chemotherapy has been shown to improve 5-year disease-free survival over those not treated with chemotherapy, based on the CALOR trial. In patients with ER-positive recurrence, hormonal therapy may be considered as it has been shown to reduce second local failures at 5 years, although overall survival was not significantly changed.

Metastatic Breast Cancer

Patients with metastatic breast cancer are unlikely to be cured of their disease. Complete remissions from systemic chemotherapy are uncommon, and only a fraction of complete responders remain progression-free for a prolonged period. The median survival for patients with stage IV breast cancer is 18 to 24 months, though a subset of patients can live for many years especially with the improvement in multimodality treatments. The typical approach to the evaluation of metastatic disease is to perform a core biopsy of the tumor for histologic confirmation of the diagnosis, stage with laboratory tests, bone scan and PET/CT to understand the full extent of the disease, then to proceed directly to systemic therapy (See Figures 2.8 and 2.9).

Most oncologists agree that once metastases have occurred, there is no survival benefit to aggressive local therapy. Recently, Badwe et al. published one of the few prospective trials evaluating surgical resection of stage IV disease, and found no overall survival benefit. However, resection of the primary tumor in stage IV breast disease may provide palliation of bleeding, ulceration and infection in carefully selected cases and should be discussed as part of a multidisciplinary team.

Chemotherapy rarely prolongs survival and is directed at improving tumor-related symptoms and slowing the spread of the tumor. The most common site of distant metastatic spread is the bone with other common sites including the lungs, pleura, brain, liver, soft tissues, adrenal glands, and lymph nodes. Different patterns of metastases have been observed by subtype. For example, patients with rapidly growing, hormone receptor negative, and poorly differentiated tumors are likely to have metastases to visceral organs (e.g., liver, lungs, and brain), whereas patients with slowly growing, hormone receptor-positive, and well-differentiated tumors are likely to develop metastases to bone and soft tissues and are less likely to exhibit early life-threatening manifestations.

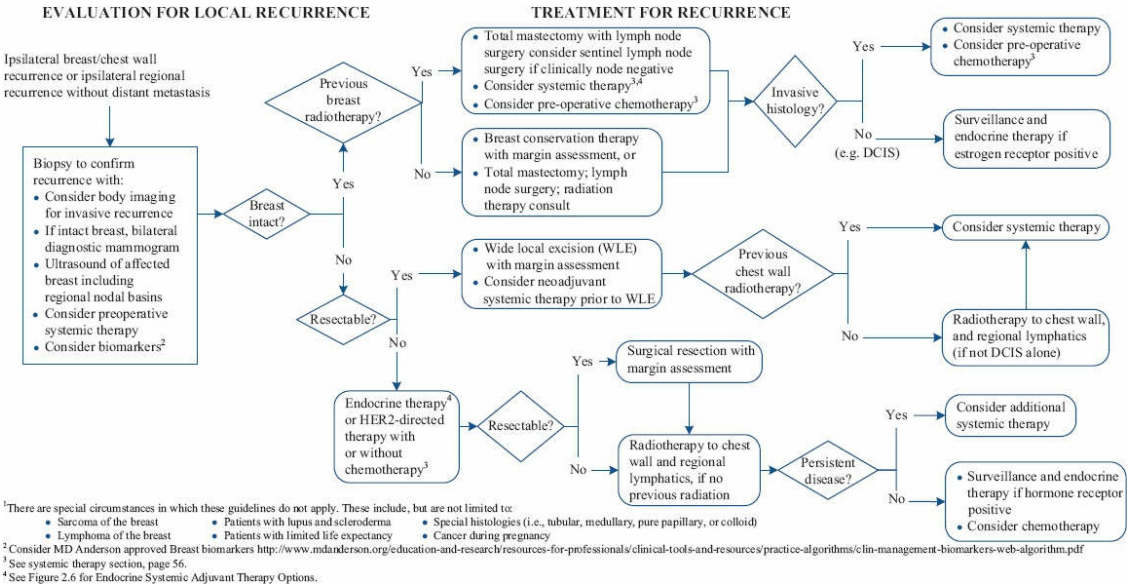


Figure 2.7 MDACC algorithm for local recurrence of invasive breast cancer.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

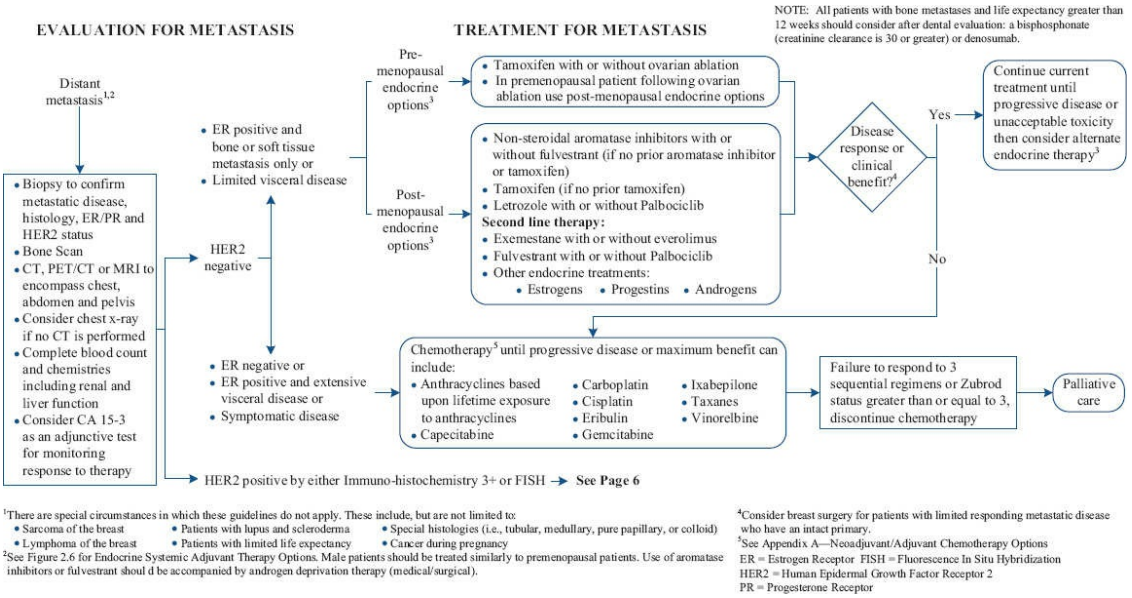


Figure 2.8 MDACC algorithm for metastatic invasive breast cancer. (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

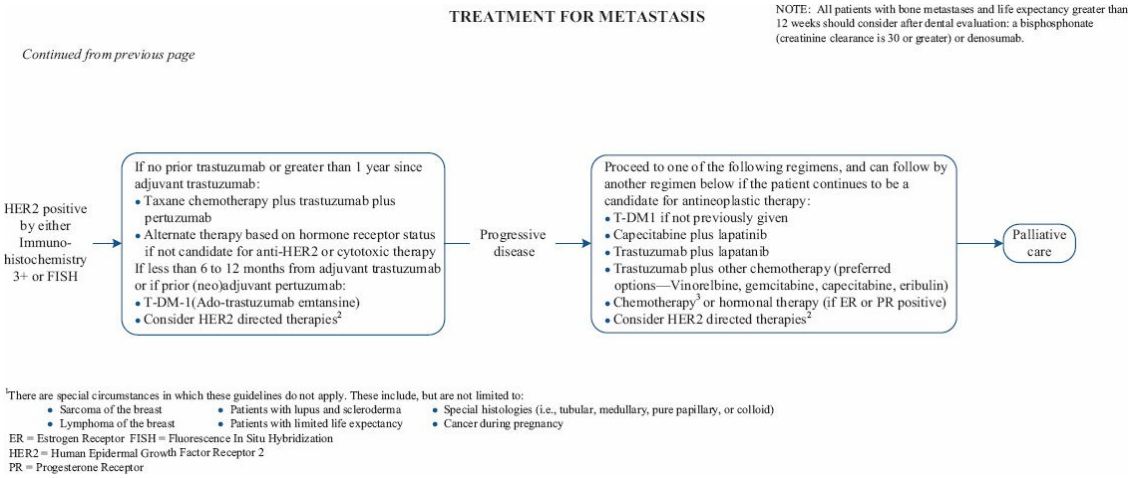


Figure 2.9 MDACC algorithm for metastatic invasive breast cancer.[1] (Copyright 2016 The University of Texas MD Anderson Cancer Center.)

For patients with metastasis, the decision to treat with systemic chemotherapy or hormonal therapy rests on several issues: the site and extent of the disease, hormone receptor status, disease-free interval, age, and menopausal status. Patients with slow-growing tumors, limited disease, and non–life-threatening metastatic disease and hormone receptor-positive or known hormone-responsive tumors are generally offered hormonal therapy as the first therapeutic modality. Because all hormonal manipulations used today have a better therapeutic ratio than do cytotoxic therapies, the practical result of sequential hormonal therapies is that patients can be actively treated with few systemic side effects. When hormonal therapy is no longer effective, these patients proceed to chemotherapy. For patients with more extensive (i.e., symptomatic) or life-threatening disease and for all patients with hormone receptor-negative breast cancer, combination chemotherapy is the first treatment of choice. Anthracyclines (e.g., doxorubicin) and taxanes (e.g., paclitaxel and docetaxel) are currently the most effective antitumor agents against metastatic breast cancer.

The choice of initial chemotherapy depends on the patient's age, performance status, prior neoadjuvant and adjuvant chemotherapy, and disease-free interval. Enrollment in clinical trials is always encouraged as novel targeted agents are actively under investigation. Trastuzumab-based chemotherapy is the standard of care for those with *HER-2/neu*-amplified tumors; however, for all other patients, combination chemotherapy has not been shown to prolong survival over sequential single agents, and it is associated with more intense side effects. Thus, outside of a clinical trial,

patients with metastatic breast cancer are typically treated with sequential single agents.

In selected patients with controlled intact primary tumor and a solitary metastasis, or multiple lesions at a single organ site, long disease-free period, and good performance status, metastasectomy may be considered, not as a standard of care, but in hopes of lengthening the DFS interval. Furthermore, in this subgroup of patients with limited metastatic disease and favorable response to systemic therapy consideration may be given to local regional therapy with surgery for the breast primary and nodal disease followed by radiation therapy as well as definitive therapy to the metastatic site(s) rendering the patient with no evidence of disease (NED) status. In a recent MDACC study by Bishop et al., 16% of patients treated with metastatic breast cancer were able to achieve NED status, resulting in 5-year OS and progression-free survival rates of 77% and 40%, respectively. This data is encouraging and shows that metastatic breast cancer patients who achieve a NED status have significantly prolonged survival with a durable response to treatment.

Special Considerations

Male Breast Cancer

Approximately 1% of all breast cancers occur in men. Diagnosis, staging and treatment strategies parallel that for women with breast cancer given the lack of randomized trials in this population. In comparison to women, men with breast cancer typically present at an older age with more advanced disease and higher nodal tumor burden. This may be because of lack of screening or awareness. The majority of tumors are located in the subareolar position presenting as a mass or nipple inversion. Diagnosis includes history, physical examination, dedicated breast imaging with mammography and ultrasound as well as core-needle biopsy. The pathology typically shows ductal histology with approximately 90% of cases estrogen receptor positive. Traditionally, men diagnosed with breast cancer have been treated with total mastectomy although breast conservation with segmental mastectomy and adjuvant radiation therapy may be an appropriate strategy with the addition of long-term mammographic surveillance. Sentinel node dissection has been shown to be accurate for axillary staging in men with clinical node-negative disease. Axillary dissection is recommended in patients with node-positive disease. Adjuvant (or neoadjuvant) systemic therapy recommendations are guided

by stage of disease and receptor status. Patients with hormone receptor-positive breast cancer are recommended treatment with tamoxifen in the adjuvant setting. A personal or family history of male breast cancer is an indication for genetic counseling as there is a higher frequency of BRCA mutation positivity in this population, particularly BRCA2 mutations.

Breast Cancer and Pregnancy

The definition of pregnancy-associated breast cancer is described as any breast carcinoma diagnosed during pregnancy, lactation, or during the first postpartum year. There is a low incidence of pregnancy-associated breast cancer, accounting for 2.8% of all breast malignancies, but breast cancer is one of the most common pregnancy-associated malignancies. Historically, the incidence is estimated at 1 in 3,000 pregnancies. These breast cancers are often identified in women at an earlier age, present as more advanced stage, and are often ER-negative, suggesting these tumors have other biologically distinct characteristics (See Figures 2.10 to 2.12).

The diagnosis of pregnancy-associated breast cancer is typically more difficult due to a low level of suspicion based on a comparatively young patient age, the relative frequency of nodular changes in the breast associated with pregnancy, and the increase in breast density during pregnancy. These difficulties in the physical examination and hormonal changes associated with pregnancy help account for a 2.5-fold increased risk for diagnosis at an advanced stage.

Both the safety and efficacy of mammography during pregnancy have been supported, with sensitivity rates from 78% to 90% in detecting suspicious features of malignancy. When the fetus is shielded adequately, the estimated fetal dose of radiation from a standard two-view mammogram is well below the threshold exposure associated with risk of fetal harm as published by the International Commission of Radiological Protection. Breast ultrasound is highly sensitive and specific in diagnosis during pregnancy and lactation, and is considered a standard method for the evaluation of a palpable breast mass. In addition, all persistent and suspicious breast masses should undergo evaluation by FNA, core-needle biopsy, or in rare cases, excisional biopsy. Excisional biopsy under local anesthesia is safe at any time during pregnancy.

Once a diagnosis of malignancy is established, treatment decisions are influenced by the specific trimester of pregnancy. The goal should be curative treatment of the breast cancer and preservation of pregnancy

without injury to the fetus. The approach to each patient must be individualized, taking into account gestational age at presentation, stage of disease, and patient preference. Termination of pregnancy in the hope of minimizing hormonal stimulation of the tumor does not alter maternal survival and is not recommended. Genetic counseling is also recommended for all women with breast cancer during pregnancy.

Surgical treatment of gestational breast cancer is generally identical to that of nongestational breast cancer. There is no evidence that extra-abdominal surgical procedures are associated with premature labor or that the typically used anesthetic agents are teratogenic. Modified radical mastectomy or breast conserving surgery with ALND as primary therapy can be undertaken at any point during pregnancy without undue risk to the mother or fetus. Although study numbers are relatively small, SLN dissection in pregnant breast cancer patients appears to be safe and accurate using 99-Tc and can be safely used in conjunction with lymphoscintigraphy.

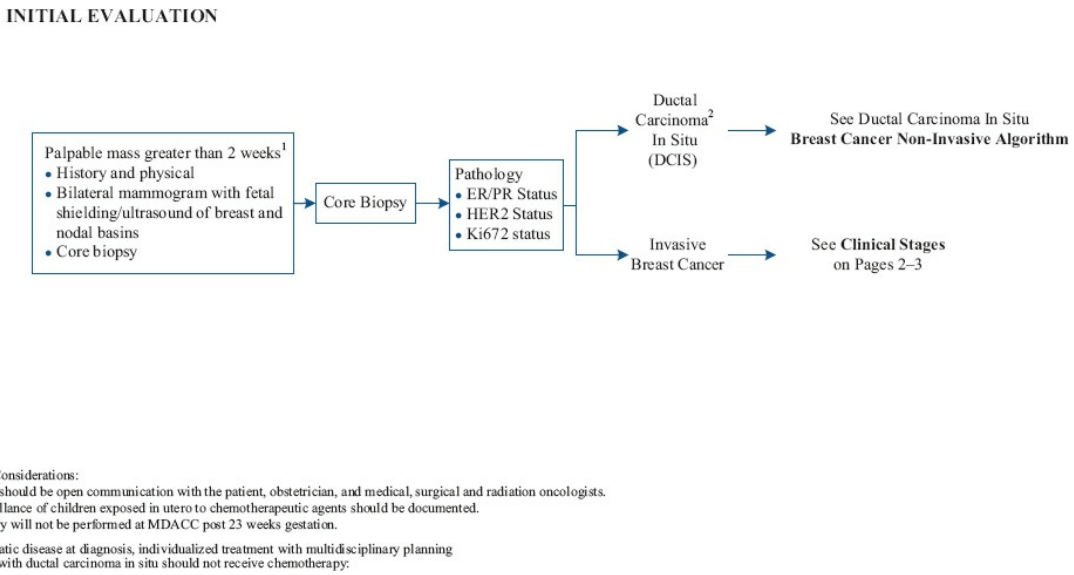


Figure 2.10 MDACC algorithm for management of invasive breast cancer in pregnancy—initial evaluation. (Copyright 2015 The University of Texas MD Anderson Cancer Center.)

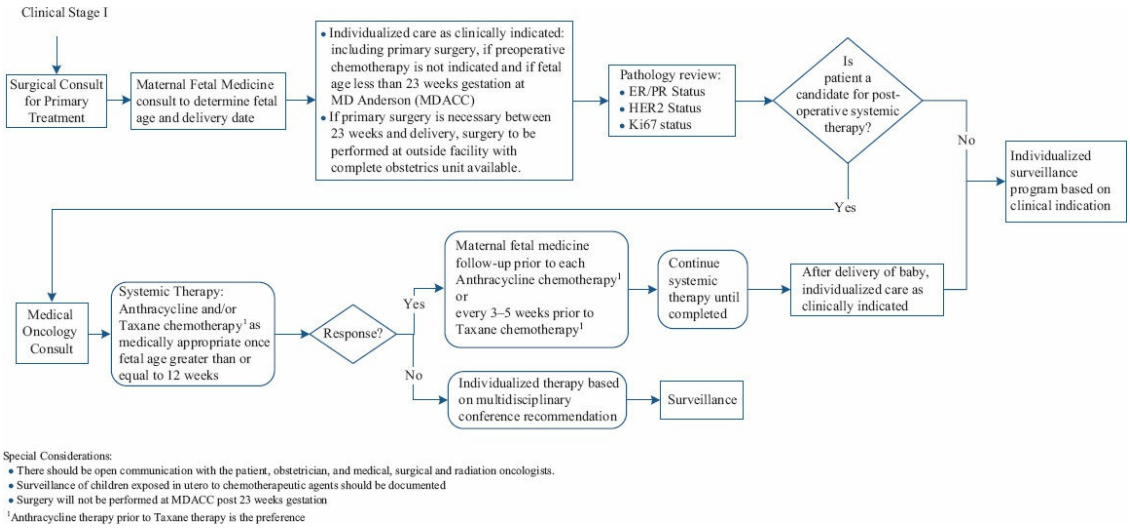


Figure 2.11 MDACC algorithm for management of invasive breast cancer in pregnancy. (Copyright 2015 The University of Texas MD Anderson Cancer Center.)

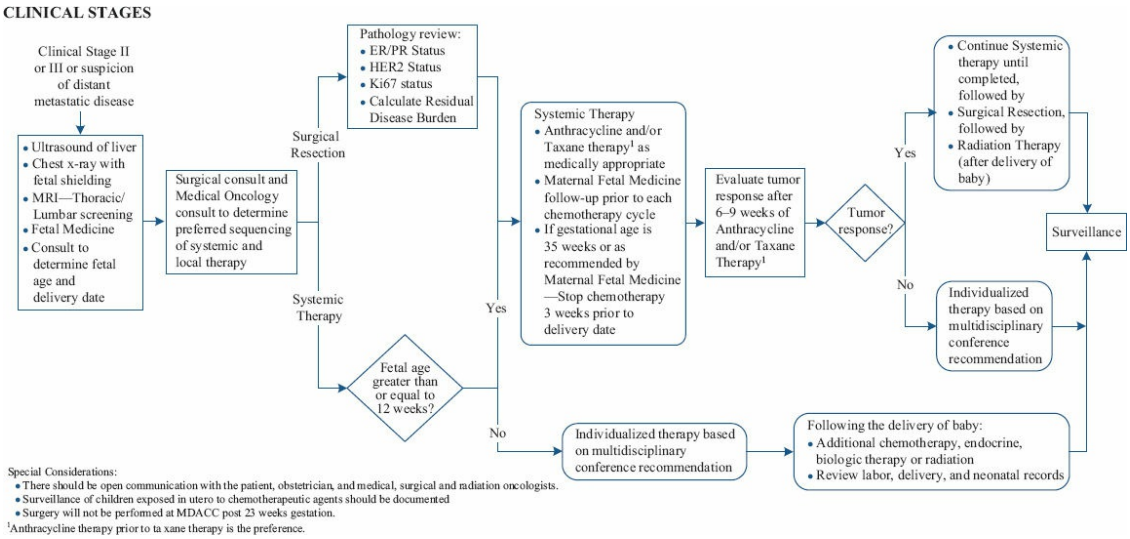


Figure 2.12 MDACC algorithm for management of invasive breast cancer in pregnancy. (Copyright 2015 The University of Texas MD Anderson Cancer Center.)

The safety of surgical intervention during pregnancy is well supported, but patients may defer until the 12th gestational week to avoid the risk of spontaneous abortion, which is highest in the first trimester. For cancer detected during the third trimester, delaying primary treatment for up to 4 weeks to allow for delivery before surgery is acceptable. If modified radical mastectomy is undertaken during pregnancy, breast reconstruction should not be performed simultaneously as reconstruction options, especially rectus or other myocutaneous flaps, are limited during pregnancy and the postpartum appearance of the contralateral breast is

unknown until after pregnancy.

For women desiring breast conservation, treatment is complicated by the fact that radiation therapy is contraindicated during pregnancy during all trimesters. For cancers detected during the third trimester, lumpectomy and axillary dissection can be performed safely using general anesthesia, and radiation therapy can be delayed until after delivery. Longer delays may be detrimental to maternal outcome, although the time limit within which radiation therapy must be carried out to minimize the risk of local recurrence is unknown.

The decision to administer neoadjuvant or adjuvant chemotherapy is difficult, as fears of congenital malformations are a serious concern for the pregnant patient. Most studies have demonstrated a safety profile and no increased risk of fetal malformation associated with chemotherapy administered during the second and third trimesters. In contrast, chemotherapy administration during the first trimester is associated with an increased incidence of spontaneous abortion, teratogenesis, or fetal malformations.

The role of endocrine therapy is contraindicated secondary to teratogenicity and possible fetal malformation. There have been reports up to a 20% incidence of fetal abnormalities, including craniofacial malformations and ambiguous genitalia, leading to the recommendation that endocrine therapy be delayed until after delivery.

Published studies have found that stage-for-stage, patients with pregnancy-associated breast cancer have similar survivals compared to those with nonpregnancy-associated breast cancer. These findings emphasize that definitive treatment and local control of breast cancer during pregnancy is not only feasible but also effective. Safe and effective treatment is available for many of these women with pregnancy-associated breast cancer.

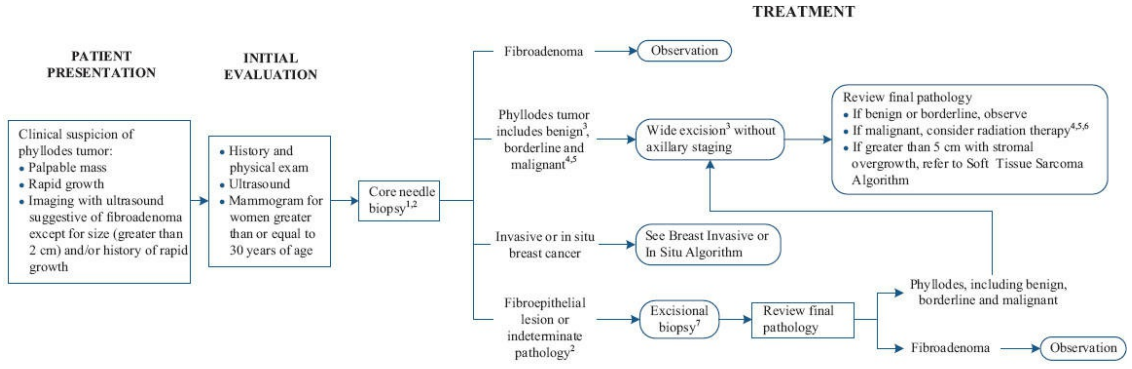
Cystosarcoma Phyllodes

Cystosarcoma phyllodes represents an uncommon fibroepithelial breast neoplasm and accounts for only 0.5% to 1% of breast carcinomas. These tumors can occur in women of all ages, including adolescents and the elderly, but most arise in women between 35 and 55 years of age. Cystosarcoma phyllodes are typically quite large and have a mean diameter of 4 to 5 cm. Because phyllodes tumors and fibroadenomas are mammographically indistinguishable, core-needle biopsy should precede

any surgical intervention. The decision to perform excisional biopsy is usually based on large tumor size, history of rapid growth, patient age, and inability to rule out an associated or obscured cancer.

Phyllodes tumors are classified as benign, borderline/low-grade malignant, or malignant based on mitotic activity, type of margin, stromal overgrowth, and cellular pleomorphism. More than 50% of these tumors are benign, and 25% are malignant. Common sites of metastases from malignant cystosarcoma phyllodes are lung, bone, and mediastinum (See Figure 2.13).

Appropriate treatment for phyllodes tumors is complete surgical excision with a negative margin, and breast conservation surgery with appropriate margins is the preferred primary therapy. Traditionally a 1-cm margin was recommended however, in patients with benign phyllodes complete excision with a negative margin is adequate. The incidence of local recurrence ranges from 5% to 20% for benign tumors and 20% to 40% for malignant tumors. Local recurrences are typically salvageable with total mastectomy and do not affect the overall survival rate. For all phyllodes tumors, the low incidence of axillary nodal metastases (less than 1%) obviates the need for lymphadenectomy. The reported rates of distant metastasis for patients with malignant tumors range from 25% to 40%, with the most common site of distant metastasis being the lung. The presence of stromal overgrowth may be the strongest predictor of distant metastasis and ultimate outcome, though 5- and 10-year overall survival rates are 75% to 88%, and 57% to 80%, respectively. To date, no role for radiation therapy, chemotherapy, or hormonal therapy has been established for this disease.



[1]Fine needle aspiration will not, and core biopsy may not, distinguish fibroadenoma from phyllodes tumor in most cases. (Tumor heterogenity may not allow for a definitive diagnosis as some phyllodes arise in a background of fibroadenoma.)
[2]It is recommended that the review of the pathology material be done by a pathologist who is experienced in phyllodes tumor.
[3]If initially excised with negative margin, wide local excision not required.
[4]Referral to a multidisciplinary sarcoma center for treatment recommendations is appropriate for malignant phyllodes tumor or one with stromal overgrowth
[5]For patients with malignant phyllodes tumor on pathology review, refer to Soft Tissue Sarcoma Algorithm.
[6]There is no prospective randomized data supporting the use of radiation treatment with phyllodes tumor. If the phyllodes tumor of the breast is benign or borderline histology, radiation therapy not routinely recommended after excision. If the tumor has malignant features (i.e., stromal overgrowth, cellular atypia, high number of mitoses) radiotherapy can be considered as follows:
- If mastectomy is performed and margins negative, do not recommend XRT
- If mastectomy was performed and margins were concerning/close, tumor involved the fascia or chest wall, or tumor was very large (greater than 5 centimeters), consider XRT to chest wall.
- If partial mastectomy only is performed, consider adjuvant XRT to breast, especially if margins are less than 1cm.

[7]Excisional biopsy includes complete mass removal, but without the intent of obtaining histologically negative surgical margins.

Figure 2.13 MDACC algorithm for management of phyllodes tumor. (Copyright 2015 The University of Texas MD Anderson Cancer Center.)

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3 Melanoma

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WHAT'S NEW FOR THE 6TH EDITION?

The melanoma treatment landscape has evolved at a rapid pace over the last several years; importantly, the development and subsequent U.S. Food and Drug Administration (FDA) approval of targeted, immune, and intralesional therapies has significantly expanded treatment options for many patients with advanced disease. Given the ongoing and rapid evolution of this treatment landscape, it is important that surgical oncologists stay abreast of these developments. In this chapter, we provide a primer on the multidisciplinary care of patients with melanoma across the spectrum of this disease, as well as introduce the recently published Eighth Edition American Joint Committee on Cancer (AJCC) melanoma staging system that is scheduled to be formally adopted for national reporting in January 2018.

EPIDEMIOLOGY

The incidence of invasive cutaneous melanoma continues to be a major public health concern in the United States; of concern, the rate of melanoma has risen about 3% per year in the United States over the past few decades. An estimated 87,110 cases of invasive melanoma will be diagnosed in the United States in 2017, and approximately 9,730 patients will have succumbed to this disease. Melanoma remains more than 20 times more common in whites than in African Americans. Overall, the lifetime risk of being diagnosed with melanoma is about 2.5% (1 in 40) for whites, 0.1% (1 in 1,000) for blacks, and 0.5% (1 in 200) for Hispanics. The incidence of melanoma has been increasing faster than that of nearly any other cancer over the last 30 years. The major environmental risk factor, exposure to ultraviolet (UV) radiation, is reflected in geographic and ethnic patterns of melanoma rates. There have also been changes in

the distribution and stage of melanoma at diagnosis, with an overall trend toward thinner tumors, particularly among any patients with T1/T2 melanomas, while the opposite trend is seen among patients with thick, T4 lesions.

RISK FACTORS

Identifying risk factors and estimating an individual's risk of developing melanoma can be clinically useful in determining primary prevention strategies and in directing the level of screening. Patients identified as being at high risk for melanoma may also be recruited to prevention trials.

Multiple factors can place a patient at risk for developing melanoma. Some factors are modifiable while others are inherent to the individual.

1. *Skin type:* Caucasians have at least 20 times the melanoma incidence of African Americans and five times the melanoma incidence of American Hispanics. In addition, white patients with red or blond hair, fair complexion, or blue eyes are at increased risk for melanoma.
2. *Age and Gender:* The incidence of melanoma increases with age. The incidence of melanoma is 1.7-fold higher for women than men before 49 years of age. Over age 70, the incidence of melanoma is 2.4-fold higher for men than women. In general, the incidence of melanoma is higher in men than in women. Specifically, a man's lifetime risk of melanoma development is approximately 1.5 times greater than a woman's risk.
3. *Overexposure to ultraviolet radiation (UVR) from the sun:* Overexposure of UVR from the sun has been associated with an increased risk of melanoma. Genetic sequencing data also support the role of UV *melanomagenesis.* Known to be a tumor with one of the highest mutational loads, a seminal report of the melanoma effort within The Cancer Genome Atlas Program revealed that a majority of somatic mutations in melanoma indeed have a "UV signature." Data support that damage from sunburns in childhood or even in adulthood are associated with increased risk. A correlation has been identified between the number of severe and painful sunburn episodes and the risk of melanoma; for example, patients who have a history of more than 10 severe sunburns are more than twice as likely to develop a melanoma compared to patients who have no history of sunburns.
4. *Use of indoor tanning devices:* Multiple studies support that use of an indoor tanning device is strongly also associated with increased risk

of melanoma. A systematic review by the International Agency for Research on Cancer (IARC) demonstrated a 15% increased relative risk of melanoma in individuals who had ever used a sunbed versus those who had never (RR 1.15; 95% CU 1.00 to 1.31); the dangers of indoor tanning have been corroborated by subsequent US and Australian groups. Young age of onset and higher frequency of use are key risk factors that are associated with even greater risk of melanoma. Indeed, a well-designed Minnesota case–control study showed increased risk with number of years, hours, and sessions of indoor tanning, independent of outdoor sun exposure. These researchers also found that 97% of women diagnosed with melanoma before age 30 had indoor tanned. An Australian population-based study showed that tanning bed use more than 10 times per year was associated with a doubling of melanoma risk in patients at least 30 years of age, and the association was stronger with earlier exposure. Young patients who use indoor tanning devices more than 10 times annually have more than 7 times the melanoma risk compared to individuals who do not indoor tan. A recent meta-analysis estimated a 1.8% increased melanoma risk for each additional tanning bed session. Since 2009, the World Health Organization lists tanning beds as a Class I carcinogen.

5. *Previous melanoma:* Individuals with a personal history of melanoma have an increased risk of developing a second melanoma of approximately 3% to 7%.
6. *Benign nevi:* Although a benign nevus is most likely not a precursor of melanoma, the presence of large numbers of nevi has been consistently associated with an increased risk of melanoma. Persons with ≥50 nevi, all of which are >2 mm in diameter, have 5 to 17 times the melanoma risk of persons with fewer nevi. Individuals who tend to develop freckles also have an increased risk of melanoma.
7. *Family history:* Approximately 10% of individuals diagnosed with melanoma have a family member with a history of melanoma. A family history of melanoma increases an individual’s risk of melanoma three- to eightfold. Furthermore, persons who have two or more family members with melanoma are also at a particularly high risk.
8. *Genetic predisposition:* Approximately 8% to 12% of melanomas occur in individuals with a genetic predisposition. Specific genetic alterations have been implicated in the pathogenesis of melanoma. Cyclin-dependent kinase inhibitor 2A (CDKN2A) is the most

commonly identified mutation in suspected familial melanoma. A tumor suppressor gene located on chromosome 9p21, CDKN2A is probably involved in familial and sporadic cutaneous melanoma. Data from North America, Europe, and Australia correlate germline CDKN2A mutation (45%, 57%, and 20%, respectively) with multiple-case families, early age of onset, and multiple primaries within an individual patient. Deletions or rearrangements of chromosomes 10 and 8p are also well documented in cutaneous melanoma. Also associated with an increase in melanoma incidence are copy number gains of chromosomes 2, 6p, 7, 8, 17, 19, and 20. These melanomas also tend to present at an earlier age and individuals may have multiple primary lesions.

9. *Atypical mole and melanoma syndrome:* Previously known as dysplastic nevus syndrome, atypical mole and melanoma syndrome is characterized by the presence of multiple, large (>5 mm) atypical dysplastic nevi generally in nonexposed areas of skin that represent a distinct clinicopathologic type of melanocytic lesion. Melanomas can originate from either normal skin or from a dysplastic nevus. Since the actual frequency of an atypical mole progressing to melanoma is small, resection of all dysplastic nevi is not indicated. However, new, changing, or symptomatic lesions that appear suspicious for melanoma on clinical and/or dermoscopic examination should be evaluated histologically.

CLINICAL PRESENTATION

Clinical features of melanoma often include variegated color, irregular raised surface, irregular perimeter, and surface ulceration. A biopsy should be performed on a pigmented lesion that changes in size, configuration, or color. The so-called *ABCDE*s are a mnemonic device to help clinicians and laypersons remember potential early signs of melanoma. *A* denotes lesion asymmetry, *B* border irregularity, *C* color variegation, *D* diameter greater than 6 mm, and *E* a lesion that is elevating, evolving, or enlarging.

When a patient presents with a lesion suggestive of melanoma, in addition to biopsy, a thorough physical examination must be performed, with particular emphasis on the skin (including the scalp, interdigit webspace, and intertriginous areas), nodal basins, and subcutaneous tissues (see also “Staging” section below).

DIAGNOSIS

The choice of biopsy technique varies according to the anatomical site as well as the size and shape of the lesion. Particular attention should be placed on the impact of the biopsy on definitive surgical treatment. Either an excisional biopsy or an incisional biopsy using a scalpel or punch is acceptable. Entire removal of the lesion is generally preferred to allow for accurate pathologic evaluation. Punch biopsies can be performed for most lesions. Generally, they can be performed when lesions are located on areas where maximum preservation of surrounding skin is important, or can be completely excised with a punch. Punch biopsies should be performed at the most raised or darkest area of the lesion to sample the most aggressive area of the potential melanoma. Full-thickness biopsy into the subcutaneous tissue should be performed to ensure accurate staging of the lesion (see the T Category section later in this chapter). An excisional biopsy allows the pathologist to accurately determine the thickness of the lesion, since the entire lesion is available for evaluation. Excisional biopsies should be performed when the lesion is too large for a punch but still can be removed without excessive surgical intervention. For excisional biopsies, a narrow margin of normal-appearing skin (1 to 3 mm) is taken with the specimen. An elliptical incision is often used to facilitate closure. The biopsy incision should be oriented to facilitate later wide excision (e.g., axially on extremities) and minimize the need for a skin graft to provide wound closure at the time of wide excision.

Shave biopsy is generally discouraged if a diagnosis of melanoma is being considered since incomplete assessment of tumor thickness may result if the deep margin is not cleared. If a shave biopsy is performed, a deep shave is preferable.

In general, we submit all pigmented lesions for permanent section examination and perform definitive surgery at a later time. We generally prefer image-guided fine-needle aspiration biopsy as an initial diagnostic maneuver to document nodal or other melanoma metastases, but not to diagnose primary melanomas.

PATHOLOGY

An experienced dermatopathologist is an important member of the multidisciplinary melanoma team, and contributes to the accurate diagnosis and staging of patients with melanoma. It is our practice to have

outside biopsies reviewed by our pathology staff upon referral to confirm diagnosis. Although the pathologic analysis primarily consists of microscopic examination of hematoxylin- and eosin-stained tumor, several melanocytic cell markers may also be useful to confirm the diagnosis. Two antibodies that have been widely used in immunohistochemical evaluations are S-100 and HMB-45. S-100 is expressed not only by more than 90% of melanomas, but also by several other tumors and some normal tissues, including dendritic cells. In contrast, the monoclonal antibody HMB-45 is relatively specific (yet not as sensitive) for proliferative melanocytic cells and melanoma. It is therefore often used as a confirmatory stain when the diagnosis of melanoma is being considered. Anti–MART-1 staining has also been shown to be very useful in the diagnosis of melanoma. The major histomorphologic components that should be included in a primary melanoma pathology report include Breslow thickness, ulceration status, peripheral and deep margin status, and mitotic rate (the latter using the dermal hot spot approach with units of mitoses per mm^2). Other features that are often also recorded include presence of microsatellites, histologic subtype, lymphovascular invasion, tumor-infiltrating lymphocytes (TIL), regression, neurotropism, growth phase, and the absence of epidermal component (as the latter may represent an uncommon dermal primary or a metastatic deposit).

The major histomorphologic types of melanoma are outlined below. While melanoma has been traditionally described using these categories, prognosis is more dependent upon staging than by these histomorphologic types.

1. *Superficial spreading melanomas* constitute the majority of melanomas (approximately 70%) and generally arise in a pre-existing nevus.
2. *Nodular melanomas* are the second most common type (15% to 30%). Nodular melanomas progress to invasiveness more quickly than other types; however, when depth of the melanoma is controlled for, nodular melanomas are generally associated with the same prognosis as other lesions.
3. *Lentigo maligna melanomas* constitute a small percentage of melanomas (4% to 10%). These lesions occur in sun-exposed areas. Lentigo maligna melanomas are classically located on the faces of older white women. In general, lentigo maligna melanomas are large (>3 cm at diagnosis), flat lesions and are uncommon in individuals

younger than 50 years. Given their often-ill-defined appearance, margin control can sometimes be challenging at the time of wide excision.

4. *Acral lentiginous melanomas* occur on the palms (palmar), soles (plantar), or beneath the nail beds (subungual), although not all palmar, plantar, and subungual melanomas are acral lentiginous melanomas. These melanomas account for only 2% to 8% of melanomas in white patients but for a substantially higher proportion of melanomas (35% to 60%) in darker-skinned patients. They are often large, with an average diameter of approximately 3 cm.
5. *Amelanotic melanomas* are relatively uncommon melanomas that occur without pigmentation changes; they are often more difficult to diagnose because of their lack of pigmentation. Factors such as change in size, asymmetry, and irregular borders may suggest malignancy and prompt a biopsy, but delays in diagnosis may sometimes be observed.

Morphogenetic Correlates and Mutations in Melanoma

In addition to the classical descriptions of melanomas, the ability to perform molecular profiling on tumors has added to our understanding of this complex and often heterogeneous disease. Although currently not generally reported as part of the primary staging of melanoma, genetic profiling has been widely employed in advanced disease; with advances in technology, mutational analysis is routinely performed from formalin-fixed paraffin-embedded archival tissue. This has led to new insights into the pathogenesis of this disease as well as actionable treatment strategies against specific molecular aberrations, especially in the setting of unresectable and advanced disease. Recent studies demonstrate that most melanomas have one or more mutations in essential kinase signaling pathways.

Important in melanoma is the RAS-RAF-MEK-ERK kinase-signaling pathway. Studies have consistently found that 40% to 50% of cutaneous melanomas (particularly superficial spreading melanoma) harbor mutations in a particular member of the RAF family known as BRAF. Although multiple BRAF mutations have been identified, approximately 90% consist of a point mutation at V600E that leads to an approximately 400-fold increase in the activity of the BRAF protein. Interestingly, 70% to 80% of benign nevi also harbor BRAF mutations, suggesting that

genetic alterations alone cannot fully explain the aggressive biology of melanoma. In the same kinase pathway, approximately 15% to 26% of melanomas are found to have an activating NRAS mutation. A comprehensive molecular analysis of cutaneous melanoma by The Cancer Genome Atlas (TCGA) melanoma project has provided new insights into the roles and frequency of mutated cancer genes and other genomic signatures. These findings helped to establish that cutaneous melanoma can be grouped into one of four subtypes: BRAF mutant (most common), RAS mutant, NF1 mutant, and triple-WT (wild type). Interestingly, BRAF and NRAS mutations are rarely identified simultaneously in the same melanoma tumor.

The phosphatase and tensin homolog (PTEN) protein is widely expressed throughout the human body. PTEN acts as a phosphatase to dephosphorylate phosphatidylinositol (3,4,5)-trisphosphate. The PI3 kinase-AKT pathway is the most common kinase pathway mutated in cancer. PTEN inhibits the activation of AKT; therefore, loss of PTEN results in the constitutive activation of the AKT pathway. Often, PTEN loss is found concurrently with NRAS mutations. Mutations in AKT have also been identified in melanoma.

While MAP kinase signaling pathway mutations have been commonly found in cutaneous melanomas arising in sun-exposed areas, they are infrequent in mucosal and acral lentiginous melanomas. A missense mutation in the c-KIT gene has been found in more than 20% of mucosal melanomas and more than 10% of acral lentiginous melanomas.

STAGING

The melanoma staging system continues to evolve in parallel with our understanding of this complex disease. The 8th Edition AJCC melanoma staging system was recently published. The AJCC encourages clinicians to use this revised staging system for clinical care beginning in 2017, although this revised (8th Edition) melanoma staging system will take effect nationally for tumor registrars beginning in January 2018. Some key features of the 8th Edition staging system include modifications to the T1 subcategory, more granular incorporation of satellite, in-transit, and microsatellite disease into the N category, and refinement and expansion of the M1 subcategories (described below).

T Category

Breslow tumor thickness and tumor ulceration remain the dominant prognostic factors in the T category. Breslow tumor thickness, measured in millimeters and reported to the nearest tenth of a millimeter in the 8th Edition, is determined by using an ocular micrometer to measure the total vertical height of the melanoma from the granular layer to the area of deepest penetration. Historically, Clark level of invasion was determined by assessing the extent of penetration into the dermis. Prospective data support that measurement of Breslow tumor thickness is more reproducible than measurement of Clark level and that Breslow tumor thickness is the more accurate predictor of outcome. The AJCC Melanoma Expert Panel continues to use Breslow tumor thickness cut-points of 1, 2, and 4 mm for the T categories (Table 3.1). However, in the 8th Edition of the AJCC staging system, a tumor thickness stratum of 0.8 mm plays a key prognostic role in subcategorizing T1 tumors, in contrast to previous incorporation of mitoses (as a dichotomous variable only, i.e., <1 mitosis/mm^2 vs. at least 1 mitosis/mm^2 contributed to the definition of T1a and T1b, respectively) in the 7th Edition. Specifically, in the 8th Edition, primary melanomas with a tumor thickness <0.8 mm without ulceration are designated T1a, whereas primary melanomas 0.8 to 1.0 mm or those <0.8 mm with ulceration are categorized as T1b. Despite its removal from the T category for thin melanomas, the AJCC recognizes the prognostic importance of mitotic rate in all T1-4 lesions and notes that this important covariate should be recorded (as number of mitoses/mm^2), as it will likely be included in the development of clinical tools and contemporary prognostic models.

Melanoma may also present as metastasis to a regional nodal basin, or even with distant metastatic disease, yet without evidence of a primary lesion. When there is no evidence of a primary tumor (i.e., unknown primary or completely regressed melanoma) or when thickness cannot be assessed, the AJCC (8th Ed.) categorizes these as T0 and TX, respectively.

TABLE **3.1** Definition of T Category—8th Edition AJCC Melanoma Staging System

	Primary Tumor	
T Category	**Thickness**	**Ulceration Status**
TX: Primary tumor thickness cannot be assessed	Not applicable	Not applicable
T0: No evidence of primary tumor	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Adapted from Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Switzerland: Springer; 2017:563–585. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the *AJCC Cancer Staging Manual*, Eighth Edition (2017) published by Springer International Publishing.

Primary tumor ulceration is histopathologically defined as the absence of an intact epidermis overlying a portion of the primary tumor. Importantly, ulcerated melanomas are associated with a significantly worse prognosis than nonulcerated melanomas of the same thickness. In the T category of the AJCC staging system, ulcerated tumors are designated by *b* following the numerical T. An exception to this rule is for a nonulcerated primary melanoma with a tumor thickness 0.8 to 1 mm; it is also designated by a “b” (T1b).

N Category

The N category refers to melanoma metastases to regional lymph node basins and other intralymphatic manifestations of melanoma metastasis (e.g., in-transit, satellite, and microsatellite disease) (Table 3.2). Regional nodal tumor burden is the most important predictor of survival in patients without distant disease. Overall, there is significant heterogeneity in prognosis among patients with regional disease.

Multiple studies have demonstrated that the number of pathologically involved lymph nodes is a dominant and independent predictor of outcome in patients with melanoma. The 8th Edition AJCC staging system N category continues to use 1, 2 to 3, and 4 or more regional lymph nodes to generate N subcategories. The presence of primary tumor ulceration has also been shown to be an independent adverse prognostic factor among patients with regional nodal disease, leading to its continued incorporation into the melanoma staging system. In the 8th Edition, both primary tumor thickness and ulceration are used to define N stage groups.

TABLE 3.2 Definition of N Category—8th Edition AJCC Melanoma Staging System

N Category	No. of Involved Lymph Nodes (LN)	Presence of In-transit, Satellite, and/or Microsatellite Metastases (ITM/SAT/MICRO)
NX	Regional nodes not assessed[a]	No
N0	No regional LN disease	No
N1	1 **or** ITM/SAT/MICRO with no tumor involved LN's	
N1a	1 clinically occult	No
N1b	1 clinically detected	No
N1c	No regional LN disease	Yes
N2	2–3 **or** ITM/SAT/MICRO with 1 tumor involved LN	
N2a	2–3 clinically occult	No
N2b	2–3, 1 of which was clinically detected	No
N2c	1 clinically occult or detected	Yes
N3	≥4 **or** ITM/SAT/MICRO with ≥2 tumor involved LN **or** any number of matted LNs ± ITM/SAT/MICRO	
N3a	≥4 clinically occult	No
N3b	≥4, at least 1 which is clinically detected, or presence of any number of matted LNs	No
N3c	≥2 clinically occult or detected and/or presence of any number of matted LNs	Yes

[a]Pathological N not required for T1 melanomas, use cN if sentinel node biopsy not performed.

Adapted from Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Switzerland: Springer; 2017:563–585. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the *AJCC Cancer Staging Manual*, Eighth Edition (2017) published by Springer International Publishing.

Aside from the number of tumor-involved lymph nodes, it is important to distinguish the burden of nodal disease as well as the presence or absence of in-transit, satellite, and/or microsatellite disease. Previous empiric definitions such a microscopic and macroscopic regional nodal disease have been replaced by “clinically occult” or “clinically detected” regional nodal disease, respectively. Patients who have clinically negative regional lymph nodes but pathologically documented nodal metastases (i.e., a positive sentinel node) are defined as having “clinically occult” nodal metastases (designated by the letter *a* in the N category). In contrast, patients with clinical evidence of regional nodal metastases that is confirmed on pathologic examination are defined as having “clinically detected” nodal metastases (designated by the letter *b* in the N category). Overall, survival for patients with clinically detected nodal disease is worse than for patients with clinically occult nodal disease.

Additional components of the N category include satellite, in-transit, or microsatellite disease; presence of at least one of these types of metastasis is coded by a suffix “c” in the 8th Edition N category and further stratified according to the number of tumor-involved regional lymph nodes (i.e., N1c, N2c, or N3c). Satellite and in-transit metastases are classically defined as skin or subcutaneous lesions within 2 cm of the primary tumor or more than 2 cm from the primary melanoma, respectively, but generally not beyond the regional nodal basin, and are types of non-nodal regional metastasis. Microsatellites are defined as any foci of metastatic tumor cells adjacent or deep to, and discontinuous from the primary tumor. It is important that there be an element of normal interposition tissue, that is, if only fibrosis and/or inflammation separate a suspected microsatellite from its primary, one should query where this represents regression of this intervening region. Microsatellites are also included in the N category staging system (see also Management of Locoregional Non-Nodal Disease section) (Table 3.2).

M Category

The M category refers to melanoma distant metastasis and is classified as stage IV. Within the M category, there is only one stage, M1. In contrast to the three M subcategories in the 7th Edition (M1a, M1b, and M1c), there are four subcategories in the 8th Edition AJCC melanoma staging system (Table 3.3). Distant metastases to the skin, subcutaneous tissue, or distant lymph nodes are designated M1a; they are associated with a better

prognosis than metastases to other anatomical sites. Metastases to the lungs are associated with an intermediate prognosis and are designated M1b. Visceral metastases are associated with a worse prognosis and are designated M1c. New to the 8th Edition is the addition of a subcategory for CNS metastasis (i.e., brain, spinal cord, and/or leptomeningeal disease), designated M1d. This category of disease is generally associated with worse survival compared to the other M categories. M1c now includes patients with non-CNS visceral metastasis. The subcategories reflect survival differences among patients with metastatic disease, depending on the anatomic sites of metastases.

Serum lactate dehydrogenase (LDH) level also continues to be included in the M category; an elevated LDH has been shown to adversely influence survival across patients with stage IV disease. LDH level is denoted with the suffix (0) in patients without elevation, or (1) for those with an elevated LDH (i.e., M1a(1) …M1d(1)). In patients in whom LDH level is unknown or unspecified, no suffix is added (Table 3.3).

Clinicopathologic Staging (c/pTNM)

Clinical staging includes above-noted features of the primary tumor as well as lesions and clinical and/or radiologic studies. Pathological staging involves incorporating all variables of microstaging of the primary tumor, as well as information from the surgical specimen, including treatment effect and margin status. Lymph node status is confirmed by both identification and quantification of sentinel and/or regional nodal basin involvement. Formal pathological staging is crucial to both proper classification and prognostication of patient outcome (Table 3.4).

TABLE 3.3 Definition of M Category—8th Edition AJCC Melanoma Staging System

	M Criteria	
M Category	**Anatomic site**	**LDH Level**
M0	No evidence of distant mets	Not applicable
M1	Evidence of distant mets	See below
M1a	Distant mets to skin, soft tissue incl. muscle and/or non-regional LN	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant mets to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant mets to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant mets to CNS with or without M1a, M1b or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

Adapted from Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual.* 8th ed. Switzerland: Springer; 2017:563–585. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the *AJCC Cancer Staging Manual*, Eighth Edition (2017) published by Springer International Publishing.

EXTENT OF DISEASE EVALUATION

In addition to physical examination, several adjuncts are used to determine the extent of disease. The National Comprehensive Cancer Network (NCCN) provides guidelines to evaluate for possible metastatic melanoma with imaging. For melanoma in situ, imaging studies are not recommended. For stages I–II melanoma, imaging is recommended only if there are specific signs or symptoms that need evaluation. For stage III melanoma, it is our general practice at MD Anderson to obtain baseline imaging with a chest x-ray, computed tomographic scan, PET/CT, and/or magnetic resonance imaging (MRI) of the brain. Ultrasonography with fine-needle aspiration of the associated lymph node basins may be useful

in detecting metastatic disease in lymph nodes; excisional biopsy and/or formal resection of suspicious nodes solely for diagnostic purposes is discouraged. Patients who present with suspected stage IV are generally staged with computed tomography (CT) of the chest, abdomen, and pelvis ± positron emission tomography (PET) as well as MRI of the brain. Image-guided percutaneous biopsy of concerning lesions can be used to confirm disease; excisional biopsy of suspected metastatic lesions is rarely indicated for diagnostic purposes.

TABLE 3.4 Stage Groups—8th Edition AJCC Melanoma Staging System

	Clinical Staging[a]			Pathological Staging[b]		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a/b	N0	M0
IB	T1b	N0	M0	T2a	N0	M0
	T2a	N0	M0			
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III	Any T, Tis	≥ N1	M0			
IIIA				T1a/b-T2a	N1a or N2a	M0
IIIB				T0	N1b, N1c	M0
				T1a/b-T2a	N1b/c or N2b	M0
				T2b/T3a	N1a-N2b	M0
IIIC				T0	N2b, N2c, N3b or N3c	M0
				T1a-T3a	N2c or N3a/b/c	M0
				T3b/T4a	Any N ≥ N1	M0
				T4b	N1a-N2c	M0
IIID				T4b	N3a/b/c	M0
IV	Any T	Any N	M1	Any T, Tis	Any N	M1

[a]Clinical staging includes microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
[b]Pathological staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes gained after partial (i.e., sentinel node biopsy) or complete lymphadenectomy.
Adapted from Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Switzerland: Springer; 2017:563–585. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the *AJCC Cancer Staging Manual*, Eighth Edition (2017) published by Springer International Publishing.

MANAGEMENT OF PRIMARY MELANOMA

Local control of a primary melanoma requires wide excision of the tumor or biopsy site—down to but generally not including the deep fascia—with a margin of normal-appearing skin (Fig. 3.1). The surgical margin is generally measured from the edge of the biopsy site or residual intact component of the lesion. The risk of local recurrence correlates more with tumor thickness than with margins of surgical excision. Thus, it is rational to vary surgical margins according to tumor thickness based on the results of numerous clinical trials over the past few decades.

Margin Width

Historically, even thin melanomas were excised with very wide margins (3 to 5 cm). Studies have demonstrated, however, that narrower margins are often associated with the same recurrence rates as wider margins.

Figure 3.1 Wide excision of melanoma. Appropriate radial margin marked schematically (center image, light gray dotted line) along with properly axially oriented elliptical incision to facilitate primary closure (inset, bottom right) after wide excision (inset, top left) (Courtesy of Gershenwald JE, Houston, TX. Copyright retained by Gershenwald and the University of Texas MD Anderson Cancer Center).

The first randomized study involving surgical margins for melanomas

less than 2 mm thick was reported by the WHO Melanoma Group. In an update of the study including 612 patients randomly assigned to a 1-cm or 3-cm margin of excision, there were no local recurrences among patients with primary melanomas thinner than 1 mm. There were four local recurrences among the 100 patients with melanomas 1 to 2 mm thick, and all four occurred in patients with 1-cm margins. There was no significant difference in survival between the 1- and 3-cm surgical margin groups. These results demonstrate that a 1-cm excision margin is safe for thin (<1 mm thick) melanomas. A multi-institutional prospective randomized trial from France compared 2- and 5-cm excisional margins in 362 patients with melanomas less than 2 mm thick. There were no differences in local recurrence rate or survival between the two groups. Similarly, a randomized trial from Sweden compared 989 melanomas patients with lesions less than 2 mm thick excised with 2- and 5-cm margins. The results were similar. With regard to thicker lesions, a randomized clinical trial from the United Kingdom, the United Kingdom Melanoma Study Group (UKMSG) Trial, compared 1- and 3-cm excisional margins in 900 patients with melanomas at least 2 mm thick. With a median follow-up time of 60 months, a 1-cm margin was associated with a significantly increased risk of locoregional recurrence (37% vs. 32% for 3-cm margins); however, overall survival (OS) was similar in the two groups. For intermediate thickness lesions, a randomized prospective study conducted by the Intergroup Melanoma Committee compared 2- and 4-cm radial margins of excision for 1- to 4-mm thickness melanomas. There was no difference in local recurrence rate between the two groups. Forty-six percent of patients in the 4-cm group required skin grafts, whereas only 11% of patients in the 2-cm group did ($P < 0.001$). Of note, however, a trend for improved 10-year disease-specific survival was seen in 4-cm margins (77%) versus 2-cm margins (70%). A clinical trial directly comparing 1- and 2-cm margins for 1- to 2-mm melanomas has not been performed. Based upon data from the WHO Trial and the Intergroup Melanoma Trial, 2-cm margins are recommended when the anatomic location is favorable and primary closure can be achieved. Since there is no demonstrable survival advantage for a 2-cm margin over a 1-cm margin in 1- to 2-mm melanomas, a 1-cm margin can be justified in cases in which a 2-cm margin is not easily achievable.

The optimal margin width for thick melanomas (>4 mm) is still unknown. A retrospective review of 278 patients with thick primary

melanomas from The University of Texas MD Anderson Cancer Center and Moffitt Cancer Center demonstrated that the width of the excision margin (≤2 cm vs. >2 cm) did not significantly affect local recurrence, disease-free survival, or OS rates after a median follow-up of 27 months. In addition, based upon data from the UKMSG Trial (investigators concluded that a 3-cm margin is better than 1-cm margin for melanomas 2 to 4 mm thick) and the Intergroup Melanoma Trial (4-cm margin is not superior to a 2-cm margin for same tumor thickness), a margin greater than 2 cm is not necessary for these thick melanomas.

Based in large part on the data from randomized, prospective trials, several recommendations can be made for margins of excision (Table 3.5). Patient with melanoma in situ, a 0.5-cm to 1-cm margin is adequate. Patients with invasive melanoma less than 1 mm thick can be treated with a 1-cm margin of excision. For patients with melanoma 1 to 2 mm thick, a simple recommendation is difficult because this patient population has been studied in several trials evaluating a range of excision margins. In general, a 2-cm margin is preferred if anatomically and functionally feasible, and in regions of anatomical constraint (e.g., the face), a 1-cm margin is sufficient. This recommendation is based on the fact that OS was similar for patients with 1- and 3-cm margins in the WHO Trial. Patients with melanoma 2 to 4 mm thick can be treated with a 2-cm margin. In patients with a melanoma thicker than 4 mm, a 2-cm margin is probably safe and is generally employed, although no prospective randomized trials have specifically addressed this thickness group.

Wound Closure

If there is any question about the ability to achieve suitable wound closure, a plastic or reconstructive surgeon should be consulted. Options for closure include primary closure, skin grafting, and local and distant flaps.

TABLE 3.5 Summary of Recommendations for Primary Melanoma Excision Margins

Tumor Thickness	Excision Margin
<1 mm	1 cm
1–2 mm	1–2 cm
2–4 mm	2 cm
>4 mm	2 cm[a]

[a]No randomized prospective trials have specifically addressed this cohort.
From Ross MI, Gershenwald JE. Evidence-based treatment of early-stage melanoma. *J Surg Oncol* 2011;104(4): 341–353.

Primary closure is the method of choice for most lesions, but it should be avoided when it will distort the appearance of a mobile facial feature or interfere with function. Many defects can be closed using an advancement flap, undermining the skin and subcutaneous tissues to permit primary closure. Primary closure usually requires that the longitudinal axis of an elliptical incision be approximately three times the length of the short axis. The skin and subcutaneous tissue are removed down to but generally not including the fascia. Closure of the wound edges is usually performed in two layers—a dermal layer of 3-0 or 4-0 undyed absorbable sutures and either interrupted skin closure using 3-0 or 4-0 nonabsorbable sutures or a running subcuticular skin closure using 4-0 monofilament absorbable sutures. Three layers are sometimes used, particularly for primary melanomas of the back. After excision, the specimen should be oriented for permanent assessment of histologic margins.

Application of a skin graft is one of the simplest reconstructive methods used for wound closure. Split-thickness skin grafts are used most commonly. For lower extremity primary lesions, split-thickness grafts should be harvested from the contralateral extremity. In general, skin grafts should be harvested from an area remote from the primary melanoma and outside the zone of potential in-transit metastasis. A full-thickness skin graft can provide a result that is both more durable and of higher aesthetic quality than a split-thickness graft. Full-thickness grafts have most commonly been used on the face, where aesthetic considerations are most significant. Donor sites for full-thickness skin graft to the face should be chosen from locations that are likely to match the color of the face, such as the postauricular or preauricular skin or the supraclavicular portion of the neck.

Local flaps offer numerous advantages for repair of defects that cannot be closed primarily, especially on the distal extremities and on the head and neck. Color match is excellent, durability of the skin is essentially

normal, and normal sensation is usually preserved. Transposition flaps and rotation flaps of many varieties have been used successfully, although for patients with high risk of in-transit metastasis, extensive flap reconstruction may significantly alter regional lymphatics.

Distant flaps may be considered when sufficient tissue for a local flap is not available and when a skin graft would not provide adequate wound coverage; myocutaneous flaps and free flaps can be used. Nonetheless, use of wound VAC-based approaches to facilitate granulation tissue that serves as a healthy tissue bed for subsequent skin graft can often obviate the need to consider such a reconstructive option (e.g., melanoma arising on the heel of the foot). Further discussion of such complex methods is beyond the scope of this chapter, but these techniques are familiar to plastic and reconstructive surgeons and are discussed in greater detail in Chapter 25.

Special Anatomic Considerations

Fingers and Toes

Most subungual melanomas involve either the great toe or the thumb. A melanoma located on the skin of a digit or beneath the nail is excised by wide excision, with distal digit lesions generally approached by concomitant partial digit amputation, the level of which is determined by extent of tumor and location. In general, amputations are performed at the distal or middle interphalangeal joint of the fingers or proximal to the interphalangeal joint of the thumb. More proximal amputations are not associated with improved survival. For melanomas of the great toe, the amputation can generally be performed proximal to the interphalangeal joint. Melanoma arising between two digits can usually be treated by wide excision with the defect reconstructed with a flap or skin graft.

Sole of the Foot

Excision of a melanoma on the plantar surface of the foot often produces a sizable defect in a weight-bearing area. When oncologically possible, deep fascia over the extensor tendons should be preserved as a base for skin graft coverage. A plantar flap, which can be raised either laterally or medially, can provide well-vascularized local tissue for weight-bearing areas, while also providing some sensation. Staged closure of some plantar melanomas, particularly of the heel, has been performed with initial use of a vacuum-assisted closure device to stimulate granulation tissue followed

by staged skin graft application. Such an approach often obviates the need for complex reconstruction and has essentially eliminated the need for extensive flap reconstruction of the heel.

Face

Because of numerous functional and cosmetic considerations, facial lesions often cannot be excised with more than a 1-cm margin. Tumor diameter, tumor thickness, and tumor location must all be considered when margin width is planned. Radiation therapy can be considered as an adjunct when margins are closer than desired. Mohs microsurgery has been proposed by some dermatologic surgeons, particularly for lentigo maligna melanoma of the face, as a means to excise melanoma with a minimal surgical margin. With this technique, resection occurs with serial histologic evaluations until the entire lesion is removed. Currently, there is a paucity of data to support an approach of Mohs microsurgery in place of standard surgical approach.

Breast

Wide excision with primary closure is the treatment of choice for melanoma on the skin of the breast; mastectomy is not generally recommended.

Umbilicus

Melanomas near or in the umbilicus may require resection of the umbilicus. In these cases, rotational flaps can often be used to reconstruct the umbilicus.

Mucosal Melanoma

Patients with true mucosal melanoma—including melanoma of the mucosa of the respiratory tract, vagina, and anal canal—historically have a poor prognosis. Because of their relative scarcity, few clinical trials have evaluated treatment options. We usually do not recommend an aggressive surgical approach to patients with clinically localized disease. In particular, we generally recommend local excision of anal melanomas rather than abdominoperineal resection. Abdominoperineal resection is associated with greater morbidity, leaves the patient with a permanent colostomy, offers no survival advantage, and does not treat at-risk inguinal nodes unless the procedure is combined with groin dissection. Adjuvant

radiation therapy may be administered to patients with mucosal melanoma in an attempt to decrease the risk of locoregional recurrence.

MANAGEMENT OF REGIONAL DISEASE

Regional lymph nodes are the most common site of melanoma metastasis. Lymph node involvement is categorized as clinically occult or clinically detected. Effective palliation and sometimes cure can be achieved in patients with regional metastases. Fine-needle aspiration or core biopsy can usually yield a diagnosis in patients who develop clinically enlarged regional nodes. Incisional or excisional biopsy is rarely indicated for diagnostic purposes.

Historical Perspective

The management of clinically occult regional lymph nodes has been the focus of a long and sometimes contentious debate. Historically, some surgeons preferred to perform lymphadenectomy only for clinically demonstrable nodal metastases. This type of excision has been termed *delayed* or *therapeutic lymph node dissection* (TLND). Other surgeons chose to excise the nodes even when they appeared normal in patients who are at increased risk of developing nodal metastases. This excision has been termed *immediate*, *prophylactic*, or *elective lymph node dissection* (ELND). Since the 1990s surgeons have generally employed a selective approach to regional lymph node dissection by employing the technique of intraoperative lymphatic mapping and sentinel lymph node (SLN) identification originally developed by Morton and colleagues for patients with clinically negative regional nodes who present primary melanoma deemed to have sufficient risk of harboring occult regional node metastases (see section on Intraoperative Lymphatic Mapping and Sentinel Lymph Node Biopsy).

With TLND, only patients with known metastases undergo a formal lymphadenectomy; this reduced the number of potentially unnecessary lymphadenectomies. The disadvantage of TLND is that delaying treatment until lymph node metastases are clinically detected may result in patients having distant micrometastases at the time of lymphadenectomy. Chances for a survival benefit associated with such an approach may therefore be diminished.

In contrast, ELND had the theoretical advantage of treating melanoma

nodal metastases at a relatively early stage in the natural history of the disease. The disadvantage of ELND is that most patients offered the procedure did not have nodal metastasis. Advocates of ELND argued that patients with clinically negative, histologically positive lymph nodes at ELND had a better chance for survival (50% to 60%) than did patients in whom the regional lymph nodes were not dissected, and clinically apparent metastases developed in the regional lymph nodes during follow-up (15% to 35%). None of the four randomized, prospective studies assessing ELND have demonstrated an OS advantage for this technique. Two trials, one from the WHO and another from the Mayo Clinic, were ultimately criticized because their study populations were at low risk for occult nodal disease, and patients were therefore unlikely to benefit from the proposed surgical treatment.

Although ELND did not offer a survival benefit to all patients, two prospective randomized trials that targeted higher-risk, clinically node-negative patients suggested that ELND may have some survival benefit in certain patient subgroups. In the WHO ELND Trial, patients with truncal melanoma at least 1.5 mm thick were randomized to wide excision and ELND versus wide excision and observation. Updated results from this trial demonstrated that patients in the ELND treatment arm who were found to have microscopic nodal disease at ELND had better OS than did patients in whom palpable lymphadenopathy developed after wide excision alone. The long-term results of the Intergroup Melanoma Trial were similar. In this trial, patients with intermediate-thickness melanomas (1 to 4 mm) who underwent wide excision and ELND were compared to a similar group of patients who underwent wide excision alone followed by observation of the regional nodal basin. Although this trial did not demonstrate a difference in overall 10-year survival rates, four prospectively selected subgroups were found to have significantly better 10-year survival with ELND than with nodal observation: patients whose primary tumors were nonulcerated (84% vs. 77%, $P = 0.03$); patients with primary tumor thickness between 1 mm and 2 mm (vs. thicker) (86% vs. 80%, $P = 0.03$); patients with extremity (vs. truncal) melanoma (84% vs. 78%, $P = 0.05$); and patients younger than 60 years (81% vs. 74%, $P = 0.03$). The results of a multicenter trial from Germany also demonstrated an absolute survival advantage, of at least 13%, for patients with positive nodes detected by sentinel lymph node biopsy (SLNB) compared to patients with positive nodes detected during observation of the nodal

basin. Although this analysis was retrospective, the results were consistent with the findings of the WHO study.

Taken together, these data called into question some historical recommendations to delay lymphadenectomy until palpable nodal disease develops; the data also supported the use of alternative approaches to permit earlier identification of occult nodal disease. A more rational, selective approach—lymphatic mapping and SLNB—has now been widely adopted. Overall, this technique satisfied many proponents of both ELND and TLND.

Intraoperative Lymphatic Mapping and Sentinel Lymph Node Biopsy

Beginning in the 1990s after its introduction by Morton and colleagues, several investigators proposed intraoperative lymphatic mapping and SLNB as a minimally invasive procedure for identifying approximately 15% to 20% of patients offered the procedure who harbor occult microscopic disease. This approach is sometimes termed *selective lymphadenectomy*.

Several studies have demonstrated that the SLNs are the first nodes to contain metastases, if metastases are present, and thus the pathologic status of the SLNs reflects that of the entire regional nodal basin. If the SLN lacks metastasis, the rest of the regional lymph nodes are unlikely to contain disease, and a completion lymphadenectomy need not be performed. Multiple studies have demonstrated that the immediate false-negative rate for SLNB is less than 5%. Other studies have confirmed the validity of the SLN concept and the accuracy of SLNB as a staging procedure. It is imperative, however, that the surgeon employing SLNB has adequate pathology and nuclear medicine support.

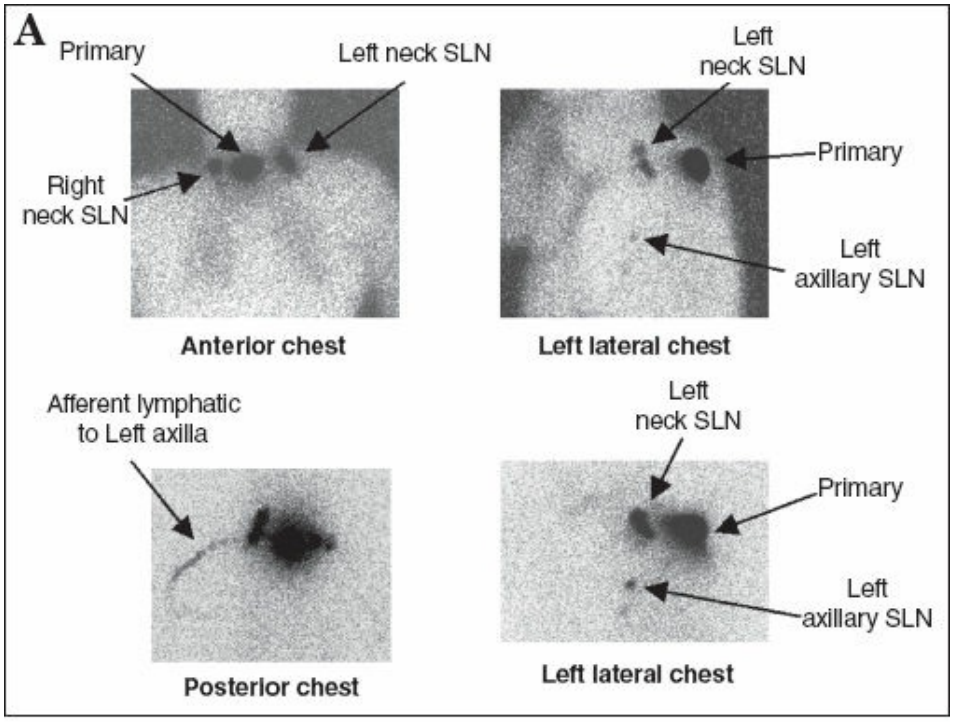
Sentinel Lymph Node Biopsy Technique

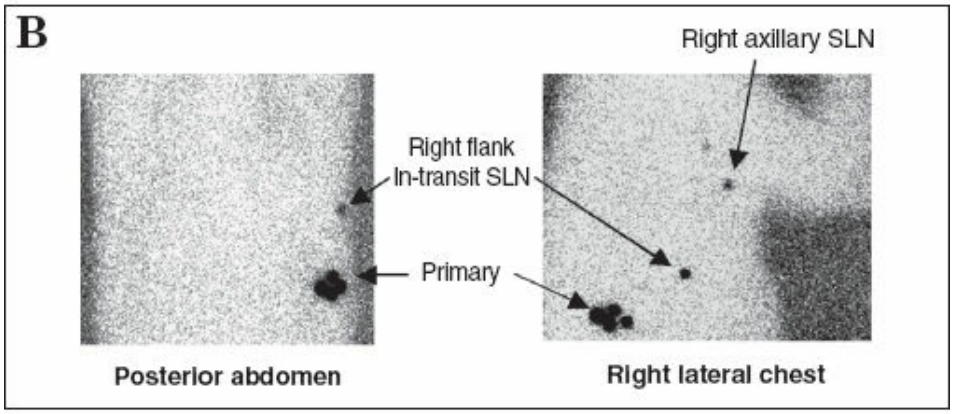
It is strongly preferred that lymphatic mapping and SLNB be performed at the time of wide excision of the primary melanoma. If a wide excision has already been performed, SLNB can still generally be performed with equivalent accuracy; however, prior extensive reconstruction of the primary melanoma wide excision site (e.g., by extensive rotational flap reconstruction) that alters lymphatic pathways in the region may significantly reduce the accuracy of this technique if performed after wide excision in such patients. Since the introduction of lymphatic mapping and

SLNB, the technique has undergone several refinements that have resulted in improved detection of SLNs. Use of a vital blue dye to identify SLNs has been part of the technique since its introduction. We typically use isosulfan blue 1% or *Lymphazurin* at our institution. If a patient is noted to have a significant history of allergic reactions, we may substitute methylene blue and anecdotally note overall similar results and a favorable side effect profile.

The blue dye is injected intradermally around the residual intact tumor or biopsy site. It is taken up by the lymphatic system and carried via afferent lymphatics to the SLN(s). The draining nodal basin is explored, and the afferent lymphatic channels and first draining lymph nodes (the SLNs) are identified by the uptake of the blue dye. With the use of blue dye alone, an approach utilized mostly in the early 1990s, an SLN was identified in approximately 85% of cases. Although this initial approach was promising, 15% of patients were unable to benefit from the procedure because no SLN was identified.

Subsequently, additional techniques were incorporated that have significantly improved SLN localization: (a) preoperative lymphoscintigraphy and (b) intradermal injection of technetium-99 (^{99}Tc)-labeled sulfur colloid accompanied by intraoperative use of a handheld gamma probe. Preoperative lymphoscintigraphy using ^{99}Tc-labeled sulfur colloid facilitates the identification of patients with multiple draining nodal basins and patients with lymphatic drainage to SLNs located outside standard nodal basins, including epitrochlear, popliteal, and ectopic/interval/in-transit sites (Fig. 3.2). In patients with melanomas that drain to multiple regional nodal basins, the histologic status of one draining basin does not predict the status of other basins. In one study, among 54 patients who underwent SLNB of an unexpected nodal site, 7 (13%) had lymph node metastases in that location. In four of the seven patients, the only positive SLN was from the unusual site. Therefore, it is particularly important to identify and assess all at-risk regional nodal basins to properly stage the disease. An advance from traditional nuclear imaging is the use of single-photon emission computed tomography (SPECT) imaging merged with CT. SPECT/CT facilitates localization of SLNs by overlaying radiotracer uptake activity onto the noncontrast CT image and is particularly helpful in the head and neck region. In one study, the surgical approach was revised on the basis of results of SPECT/CT imaging in up to 30% of cases.


A
Primary
Left neck SLN
Right neck SLN
Anterior chest
Left neck SLN
Primary
Left axillary SLN
Left lateral chest
Afferent lymphatic to Left axilla
Posterior chest
Left neck SLN
Primary
Left axillary SLN
Left lateral chest


B
Right axillary SLN
Right flank In-transit SLN
Primary
Posterior abdomen
Right lateral chest

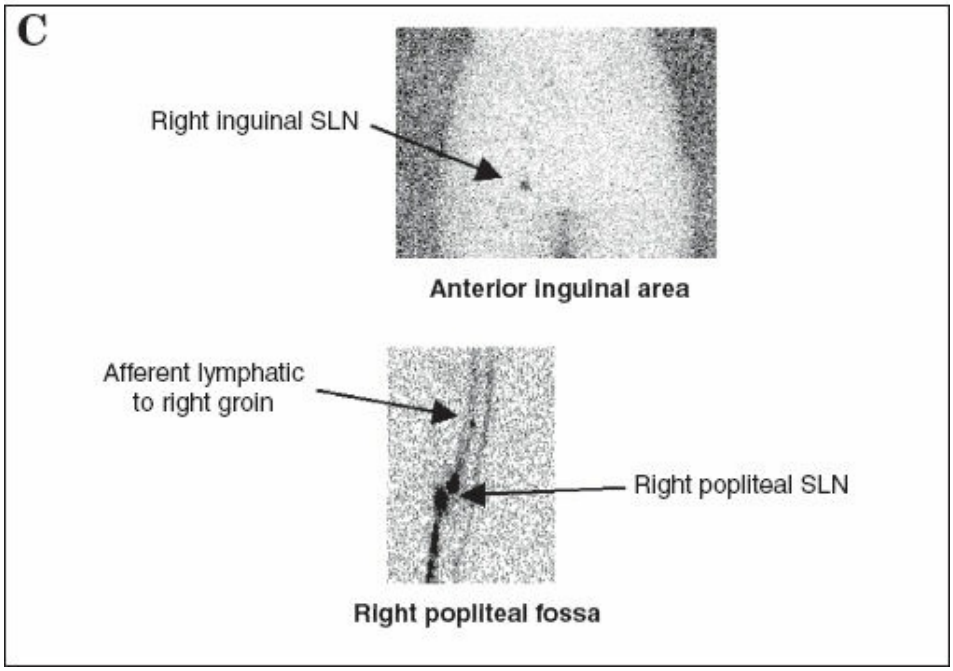

C
Right inguinal SLN
Anterior inguinal area
Afferent lymphatic to right groin
Right popliteal SLN
Right popliteal fossa

Figure 3.2 Preoperative lymphoscintigraphy. After injection of ^{99}Tc-labeled sulfur colloid at the primary cutaneous melanoma site (upper midline back), preoperative lymphoscintigraphy revealed (**A**) drainage to multiple nodal basins (bilateral neck and left axilla), (**B**) "in-transit"/ectopic sentinel lymph nodes (SLNs) in the right flank region and right axilla from a primary tumor of the right lateral back, and (**C**) SLNs in a right lower-extremity popliteal fossa lymph node basin and a right inguinal lymph node basin from a primary tumor of the heel. (Photos courtesy of Gershenwald JE. Copyright retained by Gershenwald and the University of Texas MD Anderson Cancer Center.)

Perhaps the most important development in the SLNB technique has been the introduction of intraoperative lymphatic mapping using a handheld gamma probe. In this approach, 0.5- to 1.0-mCi ^{99}Tc-labeled sulfur colloid is injected intradermally prior to surgery, either in nuclear medicine prior to arrival in the operating room or commonly after induction of general anesthesia. During surgery, a handheld gamma probe is used to transcutaneously identify SLNs to facilitate their removal. The use of both blue dye and radiocolloid increases the surgeon's ability to identify the SLN (>96% to 99% sensitivity) compared to the use of blue dye alone (≈84% sensitivity). Although most clinicians use a combined modality approach, some favor the single-agent strategy of ^{99}Tc-labeled sulfur colloid alone, and some have reported similarly excellent sensitivity compared to a combination strategy.

Incidence and Predictors of Positive Sentinel Lymph Nodes

Knowledge of the factors predictive of a positive SLN is useful for counseling patients regarding treatment options. In most studies, the overall incidence of a positive SLN among patients undergoing SLNB ranges from 15% to 20%. Multivariable analyses have revealed several factors associated with an increased risk of positive SLNs: increasing tumor thickness, ulceration, high mitotic rate, young age, and axial tumor location, with the dominant factors explored in most studies to be tumor thickness and ulceration. In one report, the incidence of a positive SLN was 4% among patients with melanomas 1 mm or thinner and 44% among patients with melanomas thicker than 4 mm (Table 3.6). In the same report, patients with ulcerated primary tumors had a higher incidence of SLN metastases compared to those with nonulcerated lesions (35% vs.

12%, respectively). The incidence of SLN metastases by AJCC clinical substage from one institutional study is shown in Figure 3.3; the incidence of a positive SLN for stages IA, IB, IIA, IIB, and IIC was 2%, 9%, 24%, 34%, and 53%, respectively.

TABLE 3.6 Rate of Positive Sentinel Node Biopsy Stratified by Tumor Thickness and Primary Tumor Ulceration (*N* = 1,375)

Tumor Thickness (mm)	Total Patients (%)	Positive SLN					P Value[b] (Ulcerated vs. Not)
		All (%)	Not Ulcerated (%)	Not Ulcerated AJCC Stage[a]	Ulcerated (%)	Ulcerated AJCC Stage[a]	
≤1.0	28	4	3	IA	16	IB	0.026
1.01–2.00	38	12	11	IB	22	IIA	0.007
2.01–4.00	23	28	25	IIA	34	IIB	0.115
>4.0	11	44	33	IIB	53	IIC	0.21
All patients	100	17	12		35		<0.0001

[a]Stage groupings calculated using tumor thickness and ulceration data only.
[b]Fisher exact test for each tumor thickness group.
SLN, sentinel lymph node; AJCC, American Joint Committee on Cancer.
Reprinted from Rousseau DL Jr, Ross MI, Johnson MM, et al. Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. *Ann Surg Oncol* 2003;10(5):569–574, with permission.

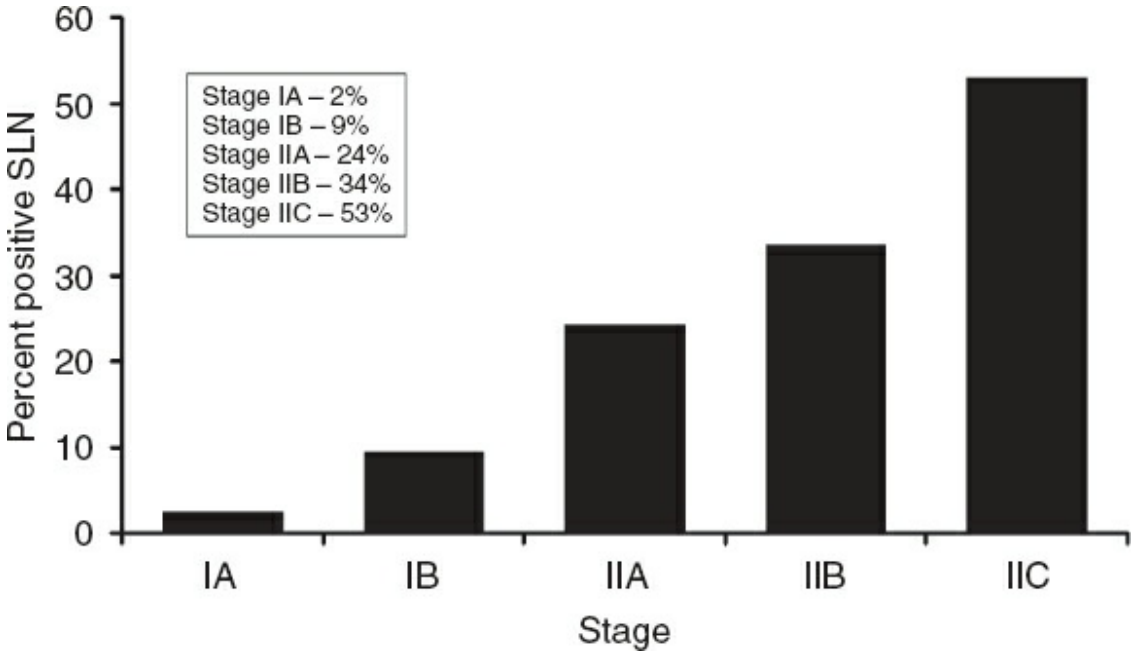


Figure 3.3 Incidence of positive sentinel lymph nodes (SLNs)

stratified by primary tumor thickness and ulceration (n = 1,375). The difference between each stage is statistically significant. The inset shows the percentage of patients with a positive SLN within each category. (Reprinted from Rousseau DL Jr, Ross MI, Johnson MM, et al. Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. *Ann Surg Oncol* 2003;10:569–574, with permission.)

Prognostic Value of Sentinel Lymph Node Status

The prognostic significance of the pathologic status of the SLN has been convincingly demonstrated. Data from The University of Texas MD Anderson Cancer Center demonstrated that SLN status was the most significant clinicopathologic prognostic factor with respect to survival in patients with melanoma. In an analysis of 1,487 patients who underwent SLNB (median tumor thickness, 1.5 mm), the 5-year survival rate for patients with positive SLNs was 73.3%, compared to 96.8% for patients with negative SLNs (Fig. 3.4). Several other multivariate regression analyses have shown that regional lymph node status is the most powerful predictor of recurrence (both regional and distant) and survival, even among patients with thick melanomas. Taken together with patients who have clinical regional disease, according to analysis of the 7th Edition AJCC database, 5-year survival rates for patients with stage III disease range from 81% for patients with only one microscopically positive lymph node and a nonulcerated primary melanoma to 29% for patients with clinically evident nodal disease with more than three pathologically involved nodes.

The prognostic importance of distinguishing between clinically occult and clinically detected lymph nodes has been emphasized by incorporation of this criterion into the AJCC melanoma staging system. The concept of tumor burden has become important in the era of SLNB as accurate microscopic staging of SLNs allows patients to be better stratified into similar risk subgroups. Several studies have shown that the diameter of the largest SLN tumor nodule and the total SLN tumor volume are significant predictors of recurrence and survival. In one study of 381 patients, Francischetto et al. found that among patients with SLN metastases of ≤0.2 mm, recurrence-free survival and overall prognosis was similar to that of patients with a negative SLN. The prognostic significance of sentinel node tumor burden continues to be an active area of investigation worldwide.

The landmark prospective Multicenter Selective Lymphadenectomy Trial-I (MSLT-1) was designed in 1994 to assess whether a selective approach to regional lymphadenectomy—limiting completion lymph node dissection to patients with microscopic disease in SLNs—confers a survival benefit compared to wide excision of the primary melanoma and observation of the regional nodal basin. Patients with primary cutaneous melanomas at least 1 mm thick or with Clark level IV or V tumors with any Breslow thickness were eligible for the trial. Two thousand and one patients were randomly assigned to wide excision alone and observation of the regional nodal basin(s) (40%) or wide excision and lymphatic mapping and SLNB (60%), with subsequent completion lymphadenectomy if any SLNs were positive.

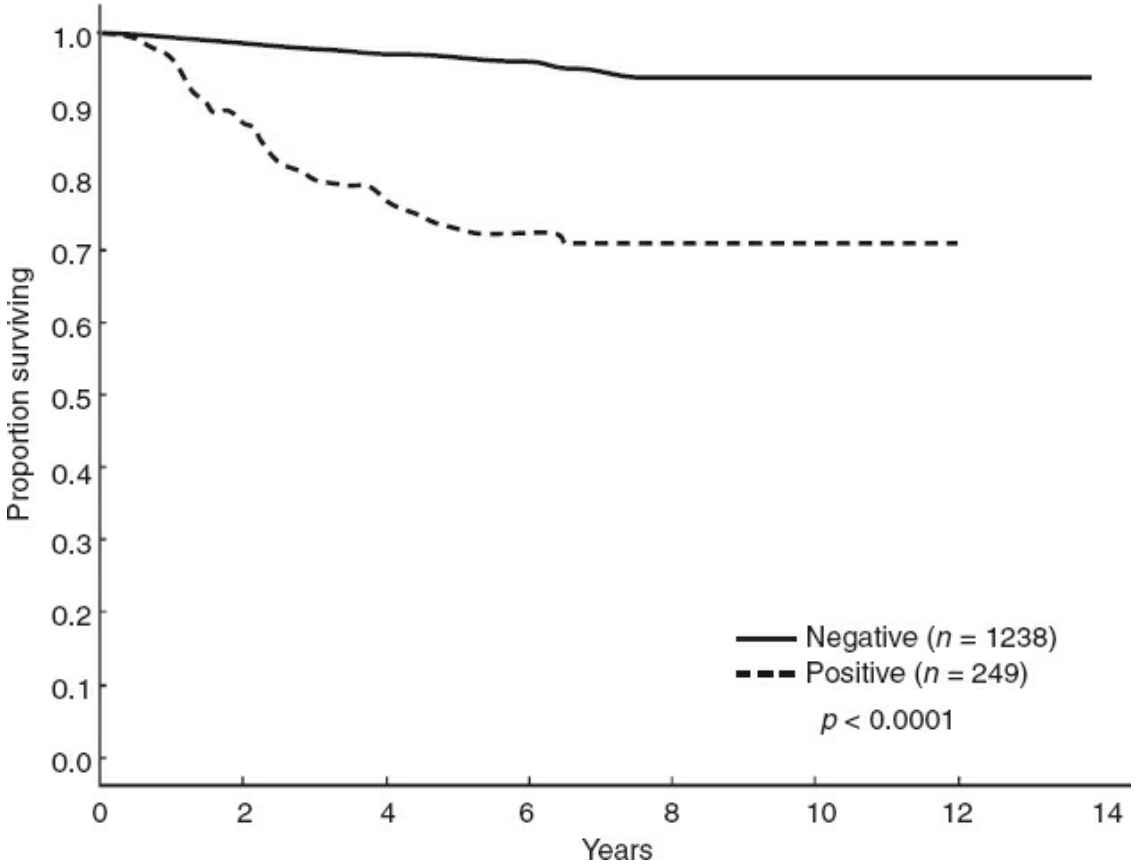


Figure 3.4 Disease-specific survival by sentinel lymph node (SLN) status in 1,487 patients. SLN status was the most significant clinicopathologic prognostic factor with respect to survival. The 5-year disease-specific survival rate was 73.3% for patients with positive SLNs, compared to 96.8% for patients with negative SLNs.

In 2014, the final trial report was published with 10 years of follow-up

data. Ten-year disease-free survival rates were significantly higher in the SLNB group than in the observation group among patients with intermediate-thickness melanomas: 71.3 ± 1.8% in the SLNB group compared to 64.7 ± 2.3% in the observation group (hazard ratio for recurrence or metastasis, 0.76; 95% CI 0.62 to 0.94; $P = 0.01$). When the SLNB group was further explored, it was noted that patients who had evidence of microscopic SLN involvement did worse than patients with a negative SLNB. For patients with intermediate thickness primary melanoma (defined in MSLT-I as 1.2 to 3.5 mm), the melanoma-specific survival at 10 years was significantly worse in patients with a positive SLNB compared to those who had a negative SLNB (62% vs. 85%, HR 3.09, 95% CI 2.12 to 4.49). For patients with thick melanoma (defined in MSLT-I as >3.50 mm), the melanoma-specific survival rate at 10 years was again significantly worse in patients with lymph node involvement compared to those who had a negative lymph node biopsy (48.0% vs. 64.6%, HR 1.75, 95% CI 1.07 to 2.87). The trial did not identify a relationship among patients with thin melanomas, but noted it had too few events to analyze.

The results of the MSLT-1 were corroborated by a larger, albeit retrospective single institution analysis by the Melanoma Institute of Australia (MIA) over a 16-year period prior to 2008. They identified patients treated wide excision alone ($N = 2,931$) versus excision along with SLNB ($N = 2,909$). Stratified univariate analysis for different subgroups indicated a significantly better melanoma-specific survival for SLNB patients with lesions >1 mm to 4 mm thick ($P = 0.011$), and an improved disease-free and recurrence-free survival in the SLNB cohort compared to the observation group (both $P < 0.001$), concluding outcome was better for patients that underwent SLNB.

Pathologic Evaluation of Sentinel Lymph Nodes

Pathologists have traditionally examined lymph nodes obtained from a lymphadenectomy by examining a hematoxylin–eosin-stained section from each paraffin block. This conventional approach, however, can miss disease in SLNs, primarily because of sampling error. In one study, 8 of 10 patients who underwent SLNB and subsequently developed regional nodal failure in nodal basins that were negative for disease according to conventional histologic examination of SLNs had microscopic disease detected when the SLNs were reassessed using specialized pathologic

techniques. Data from this and other studies suggest that failure to use specialized techniques, rather than failure to correctly identify SLNs, accounts for many cases of false-negative findings on SLNB; these studies helped to define the current standards of SLN assessment using more enhanced pathologic evaluation than had been previously performed.

With the SLNB technique, fewer lymph nodes are submitted for analysis than are submitted with formal lymphadenectomy, and the pathologist can therefore focus on only those nodes—the SLNs—that are at the highest risk. Currently, the combination of hematoxylin–eosin assessment of several levels and immunohistochemical analysis is generally considered a standard practice in assessing SLNs. Several antibodies directed against melanoma-associated antigens (S-100, HMB-45, tyrosinase, MAGE3, and MART-1) are routinely used for immunohistochemical evaluation. Because certain antibodies have low specificity (S-100) and others have low sensitivity (HMB-45, MAGE3, and tyrosinase), a panel of antibodies is commonly used. At MD Anderson Cancer Center, this panel includes HMB-45 and MART-1.

The use of frozen section for immediate evaluation of SLNs is highly controversial in melanoma. Frozen sections usually provide suboptimal morphology and may lack the subcapsular region of the lymph node (an area likely involved in SLN metastases). Also, processing of the frozen tissue requires additional sectioning and micrometastases may be lost in the discarded unexamined sections. Therefore, for SLNs from patients with melanoma, most protocols consider the examination of routinely processed material (formalin-fixed, paraffin-embedded) as the gold standard. A possible alternative is touch preparation/cytologic analysis of specimens; these approaches seem to provide accurate and cost-effective SLN assessment in some specialized centers. We feel strongly that the use of frozen section risks a lower accuracy of detection of metastatic lesions. In general, this approach is employed only if a grossly suspicious SLN is identified and if a formal preoperative discussion of possible concomitant completion lymphadenectomy has occurred.

Because even the combination of histologic and immunohistochemical examination of SLNs may fail to identify isolated melanoma cells or oligocellular deposits, some have suggested a molecular-based approach to examination of SLNs. With use of the reverse transcriptase–polymerase chain reaction (RT-PCR), it has been estimated that one melanoma cell in a background of 1×10^6 to 1×10^7 normal cells can be identified. Some

investigators have proposed, however, that this level of diagnostic sensitivity may actually overestimate clinically relevant disease. Some studies show that the prognosis of patients with an SLN that is positive by RT-PCR but negative by histologic or immunohistochemical analysis is worse than that of patients who have SLNs negative by both techniques. Although preliminary results were intriguing, the clinical significance of positive RT-PCR findings in a histologically negative SLN has not been translated into clinically relevant endpoints with additional follow-up. Therefore, these or other approaches that attempt to interrogate SLNs at the "molecular" level are therefore not currently recommended outside of the research arena or clinical trial, as the role of molecular staging in patients undergoing lymphatic mapping and SLNB is still being evaluated.

Identifying Additional Disease in Nonsentinel Nodes

Classically, patients who have a melanoma-positive SLN identified by SLNB had completion lymphadenectomy. Pathologic evaluation of completion lymphadenectomy specimens often reveals no additional disease. It is important to remember that completion lymphadenectomy specimens are routinely assessed with standard histologic techniques rather than the more rigorous approach employed for SLNB specimens. As a result, there may actually be additional disease in the completion node dissection specimen that goes undetected. This disease, in theory, represents a potential source of subsequent recurrence if it were not removed. Because such recurrences are difficult to treat surgically and may contribute to significant morbidity, completion lymphadenectomy performed for microscopic disease provides the potential for improved regional control. In addition, identifying patients with minimal disease burden by using the SLN approach may help identify the group of patients who may derive an improved survival benefit from early TLND (i.e., completion lymphadenectomy). Furthermore, knowledge of the pathologic status of the SLNs allows proper staging and thus facilitates decision making regarding adjuvant treatment. In several studies, when the non-SLNs in a completion lymphadenectomy specimen were evaluated by hematoxylin–eosin staining and immunohistochemistry, only 8% to 25% of completion lymphadenectomy specimens contained additional nodes with metastatic disease. Since most patients have metastatic disease identified only in SLNs, there has been interest in identifying patients who, despite having a positive SLN, have a low probability of metastatic disease

in non-SLNs.

In an analysis of primary tumor and SLN characteristics, the number of SLNs harvested, the Breslow thickness of the primary tumor, and SLN burden (largest focus of metastasis, total area of metastases, number of metastatic foci, and extracapsular extension) most accurately predicted the presence of tumor in non-SLNs. Although these results are intriguing and warrant further study, decisions regarding completion lymphadenectomy cannot yet be made strictly on the basis of primary tumor or SLN characteristics. Completion lymphadenectomy following identification of a positive SLN has been a standard of care for over two decades, although the lack of a defined survival benefit specifically associated with completion lymph node dissection among patients with a positive SLN has helped to usher in an era of clinical trials designed to assess this important clinical question.

The Multicenter Selective Lymphadenectomy Trial-II (MSLT-II) seeks to answer this question by randomizing patients with at least one positive SLN to nodal observation or immediate completion lymphadenectomy after a positive SLN. The trial completed accrual ($N > 1{,}900$) and survival-based endpoints have very recently been reported. Overall, at a median follow-up of 43 months, in the per-protocol analysis, the mean 3-year melanoma-specific survival (primary endpoint) was similar in both the dissection group and the observation group; disease control in the regional nodes at 3 years was also increased in the dissection group compared to the observation group (92% vs. 77%; $P < 0.001$). Nonsentinel node metastases (identified in 11.5% of the patients in the dissection group) were a strong and independent predictor of recurrence (hazard ratio, 1.78; $P = 0.005$). Taken together, these initial data support that immediate CLND increased regional disease control and provided prognostic information, but did not increase MSS in these patients with SLN metastases.

In the German multicenter, randomized, phase III DeCOG-SLT clinical trial, 483 patients with a positive SLNB were randomly assigned to immediate surgery (i.e., completion lymphadenectomy following a positive SLNB) or to regional node observation. Of note, 66% of patients had an SLN metastasis of 1 mm or less. At a median follow-up of 35 months, among 473 included in the intention to treat analysis, the authors found that there was no significant difference in their primary endpoint of 3-year distant metastasis-free survival: 77% versus 75% for the

observation versus immediate complete dissection groups, respectively (HR 1.03, 95% CI 0.70 to 1.50). However, they did report a significant difference in regional recurrence rates among the groups. Analysis is ongoing; it does appear that patients in the immediate surgery arm had better locoregional disease control, and continued follow-up will be important to further discern these relatively early survival-based endpoints. Importantly, it should be noted that the study is impacted from enrollment challenges and did not accrue its target of 556 patients, thus reducing the power of the study as initially reported (ITT analysis, *N* = 473).

Current Practice Guidelines for the Use of Sentinel Lymph Node Biopsy

Candidates for SLN biopsy include patients with newly diagnosed clinically node-negative primary cutaneous melanoma who are predicted to be at intermediate or high risk of harboring occult regional nodal disease based on primary tumor characteristics. Although uniform risk thresholds have not been completely resolved, a tumor thickness threshold of at least 1 mm has gained wide acceptance. While routine use of SLN biopsy in patients with thin (<1 mm) melanoma is not indicated because of the overall low risk of nodal involvement in this group, a selective approach to SLN biopsy for patients with thin melanoma has evolved in many centers based on the presence of established or putative adverse risk factors of the primary melanoma, and remains an area of ongoing investigation and debate. Many melanoma clinicians consider a threshold risk of approximately 5% to be sufficient in an otherwise healthy individual to offer lymphatic mapping and sentinel node biopsy, and this generally includes patients whose primary tumor thickness is >0.75 mm. Therefore, based on the most recent AJCC (8th ed.) guidelines, patients with T1b (Table 3.1) or greater melanomas can be considered for SLNB. While detailed discussion is beyond the scope of this chapter, one helpful source of information for this important clinical question that is also generally reflective of the ongoing debate can be found in the NCCN guidelines, an online resource that is generally updated at least annually.

Of note, the presence of clinically evident lymphadenopathy at the time of diagnosis obviates the need for SLNB, as these patients will generally be offered TLND in the absence of synchronous distant metastasis.

When the SLNs are negative, no further regional node surgery is performed, and the remaining regional lymph nodes are left intact. When

the SLNs show evidence of metastatic disease, completion lymphadenectomy of the affected nodal basin has been a longstanding standard of care; however, this approach has been called into question by some based on the overall lack of a survival benefit in MSLT-1, early findings reported by the DeCOG clinical trial that demonstrated no survival advantage for CLND at a median follow-up of just under 3 years, and the recently reported results from MSLT-2 that also demonstrated no overall survival advantage for CLND. This ongoing debate will likely continue as data from clinical trials, including the MSLT-II, mature and additional studies are reported.

Management of Clinically Detectable Lymph Node Disease at Presentation

For patients who present with clinically apparent or detectable disease in the regional lymph node basin, a staging work-up is recommended. Physical examination should be performed to identify lesions suspicious for additional primary melanoma, as well as to identify satellite disease and/or in-transit metastases; a thorough nodal examination should also be performed to exclude clinically suspicious nodal disease in other regional basins. Staging evaluation typically includes baseline imaging with a chest x-ray, computed tomographic scan, PET/CT, and/or MRI of the brain. This approach allows the surgeon to identify any further disseminated disease beyond the regional basin that may preclude a recommendation for lymphadenectomy. If not already excised at the time of referral, image-guided biopsy (generally with fine-needle aspiration biopsy) is preferred over excision to confirm regional disease; a similar approach may be used to document other patterns of metastasis, such as distant disease, that would alter treatment planning.

In the absence of distant metastasis, regional nodal disease has generally been approached with a recommendation for formal therapeutic lymphadenectomy followed by consideration of adjuvant therapy. Given the high risk of recurrence for such patients, our group, as well as others, has begun to explore the concept of neoadjuvant therapy for patients who present with clinical regional lymphadenopathy. For example, recent efforts by our group have focused on early molecular profiling of these patients. For BRAF V600 mutant patients, we recently completed a small proof of concept phase II randomized neoadjuvant therapy trial with presurgery dabrafenib+trametinib (a combination therapy currently

approved for unresectable or metastatic disease; see Targeted Therapy section below) followed by surgery versus surgery alone in patients with resectable stage IIIB/C disease; importantly, we observed a pathologic complete response (pCR) in 58% of patients treated on the neoadjuvant arm. Ongoing analysis will determine if pCR confers a survival advantage and whether this regimen should be further explored.

Technical Considerations

Axillary Dissection

General . Axillary dissection includes levels I, II, and III lymph nodes (Fig. 3.5). The arm, shoulder, and chest are prepped and included in the surgical field.

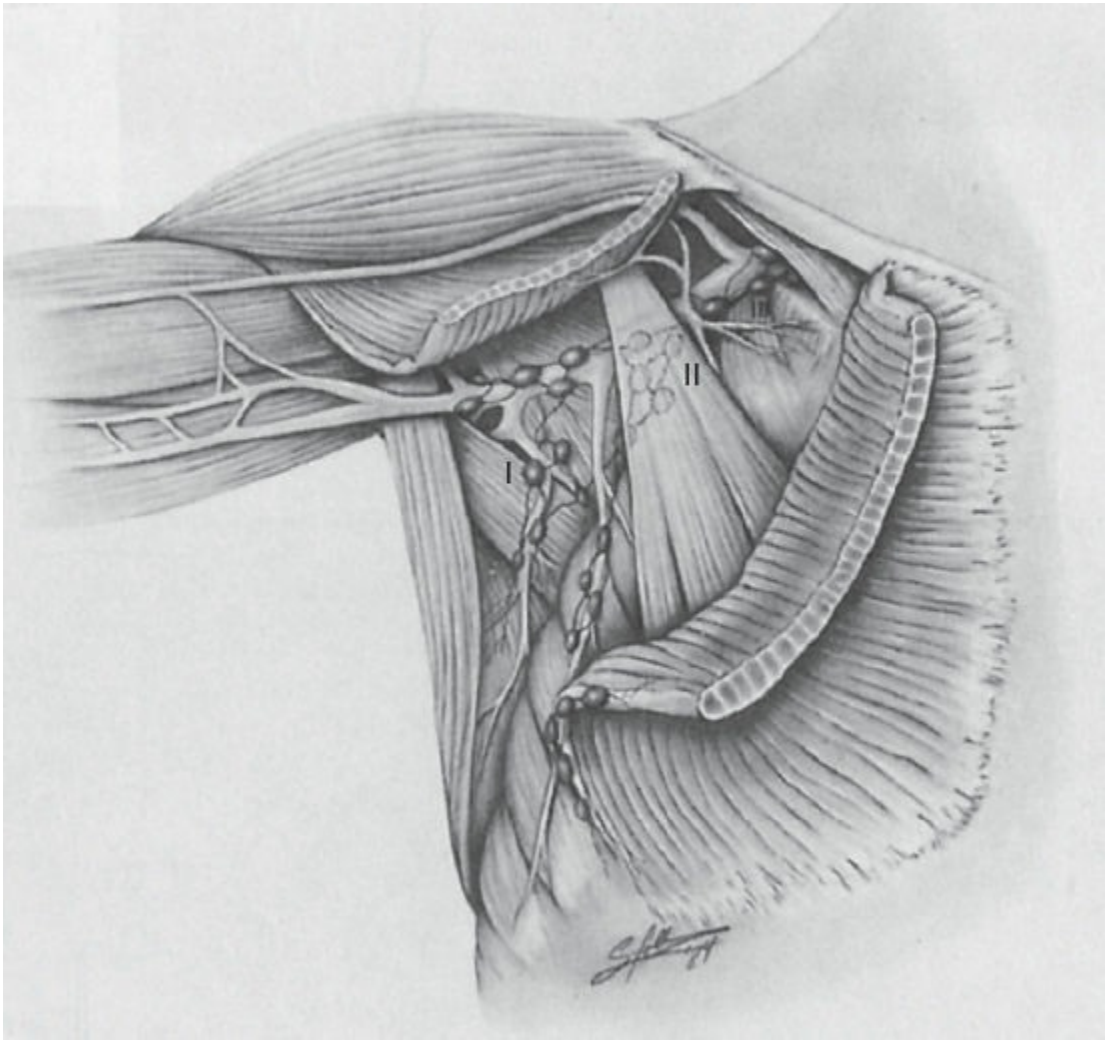


Figure 3.5 Lymphatic anatomy of the axilla showing the three groups of axillary lymph nodes defined by their relationship to the

pectoralis minor muscle. The highest axillary nodes (level III) medial to the pectoralis minor muscle should be included in an axillary lymph node dissection for melanoma. (From Balch CM, Milton GW, Shaw HM, et al., eds. *Cutaneous Melanoma*. Philadelphia, PA: Lippincott; 1985, with permission.)

Incision . We generally use a slightly S-shaped incision beginning anteriorly along the superior portion of the lateral edge of the pectoralis major muscle, traversing the axilla over the fourth rib, and extending inferiorly along the anterior border of the latissimus dorsi muscle. The incision should be constructed so that previous scars can be excised en bloc with the specimen.

Skin Flaps . Skin flaps are raised anteriorly to the lateral border of the pectoralis muscle and the midclavicular line, inferiorly to the sixth rib, posteriorly to the anterior border of the latissimus dorsi muscle, and superiorly to just below the pectoralis major insertion. The medial side of the latissimus dorsi muscle is dissected free from the specimen, exposing the thoracodorsal vessels and nerve. The lateral edge of the dissection then proceeds cephalad to the axillary vein. In a lateral to medial fashion, the thoracodorsal neurovascular bundle is skeletonized and preserved. These maneuvers generally allow the next portion of the dissection to proceed from medial to lateral. The fatty and lymphatic tissue adjacent to the pectoralis major muscle is dissected free around to its undersurface, where the pectoralis minor muscle is encountered. The interpectoral groove is exposed.

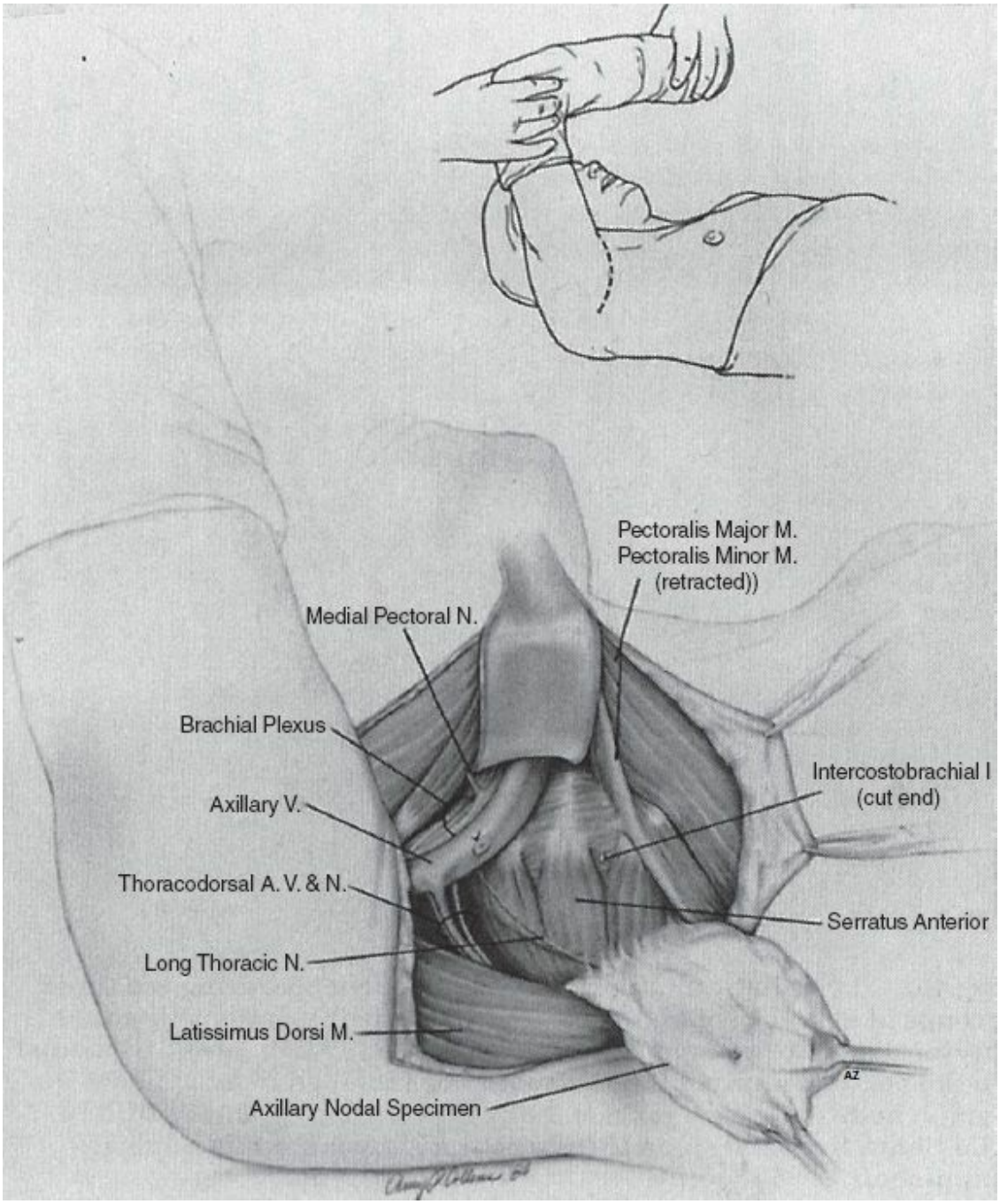


Figure 3.6 Access to the upper axilla. The arm is draped so that it can be brought over the chest wall during the operation. This facilitates retraction of the pectoralis muscles upward to reveal the level III axillary lymph nodes. (From Balch CM, Milton GW, Shaw HM, et al., eds. *Cutaneous Melanoma*. Philadelphia, PA: Lippincott; 1985, with permission.)

Lymph Node Dissection . The medial pectoral nerve is preserved. The interpectoral nodes are dissected free and lymphoareolar tissue swept from Rotter's space. At this point, the dissection generally proceeds in a lateral to medial fashion, with lymph node bearing tissue swept medially; the

thoracodorsal bundle is again visualized and the long thoracic nerve is identified and preserved. The fatty tissue between the two nerves is separated from the subscapularis muscle and included with the specimen. The upper axilla is exposed by bringing the patient's arm over the chest by adduction and internal rotation. If nodes are bulky, the pectoralis minor muscle may be divided to facilitate exposure. Dissection of the upper axillary lymph nodes should be sufficiently complete that the thoracic outlet beneath the clavicle, Halsted ligament, and subclavius muscle are seen (Fig. 3.6). Fatty and lymphatic tissues are dissected downward over the axillary vein. The apex of the dissected specimen may be tagged. The specimen is removed from the lateral chest wall. Intercostobrachial nerves traversing the specimen are sacrificed.

Wound Closure . One 15 F closed-suction catheter is usually placed percutaneously through the inferior flap into the axilla. An additional catheter may be inserted through the inferior flap depending on body habitus. The skin is closed with interrupted 3-0 undyed absorbable sutures and running 4-0 subcuticular absorbable sutures.

Postoperative Management . Suction drainage is generally continued until output is less than 30 mL per day for 2 consecutive days. By approximately 4 weeks, the suction catheters are removed, regardless of the amount of drainage, to reduce the likelihood of infection. Subsequent fluid collections are removed by needle aspiration, or on occasion by percutaneous drainage.

Superficial Groin Dissection

General . For groin dissection, the patient is placed in a slight frog-leg position with hip externally rotated and the knee partially flexed.

Incision . A lazy-S incision is made from superomedial to the anterior superior iliac spine, vertically down to the inguinal crease, obliquely across the crease, and then vertically down to the apex of the femoral triangle. Previous SLNB incisions and underlying cavities should be excised en bloc with the specimen.

Skin Flaps . The limits of the skin flaps are medially to the pubic tubercle and the midbody of the adductor magnus muscle, laterally to the

lateral edge of the sartorius muscle, superiorly to approximately 5 cm above the inguinal ligament, and inferiorly to the apex of the femoral triangle.

Lymph Node Dissection . Dissection is carried down to the muscular fascia superiorly (Fig. 3.7). All fatty, node-bearing tissue is swept down to the inguinal ligament and off the external oblique fascia. Medially, the spermatic cord or round ligament is exposed, and nodal tissue is swept laterally. Nodal tissue is swept off the adductor fascia to the femoral vein. At the apex of the femoral triangle, the saphenous vein is identified. If the saphenous vein can be preserved, nodal tissue is removed from the vessel circumferentially: otherwise, it is sacrificed. Laterally, nodal tissue is dissected off the sartorius muscle and the femoral nerve. With dissection in the plane of the femoral vessels, the nodal tissue is elevated up to the level of the fossa ovalis, where the saphenous vein is suture-ligated at the saphenofemoral junction if it is sacrificed. The specimen is dissected to beneath the inguinal ligament, where it is divided. If a component of the planned surgery, Cloquet node (the lowest iliac node) is sent as a separate specimen for frozen-section examination (Fig. 3.8).

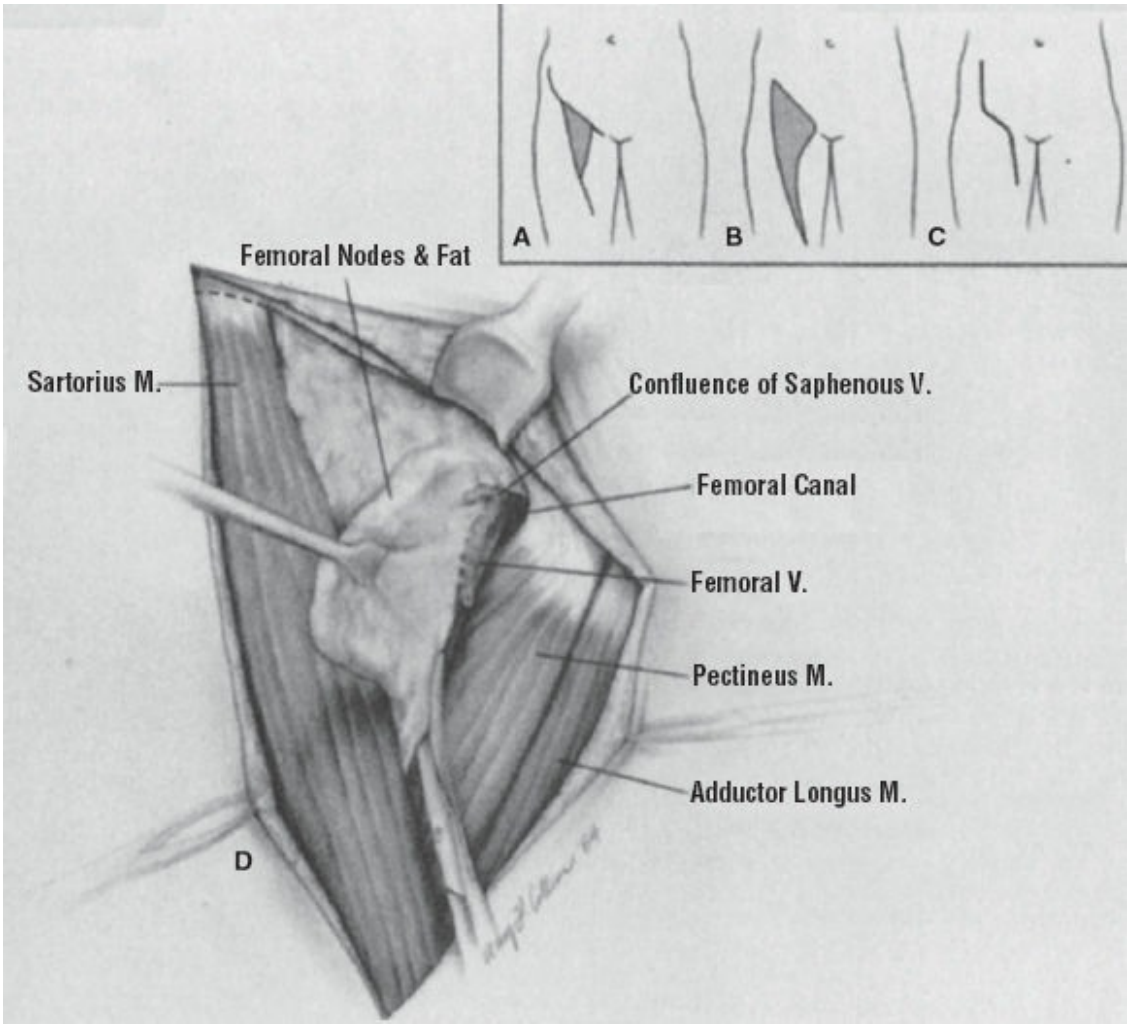


Figure 3.7 Technique of inguinal lymph node dissection. **A:** The borders of the femoral triangle are the inguinal ligament superiorly, the sartorius laterally, and, the adductor longus medially. **B:** The lymphatic contents removed during a superficial inguinal lymphadenectomy include the lymphatic contents of the femoral triangle as well as nodal tissue that lies superficial to the external oblique superior to the inguinal ligament. **C:** The lazy-S incision used for an inguinal lymphadenectomy. **D:** The anatomy visualized during an inguinal lymphadenectomy. (From Balch CM, Milton GW, Shaw HM, et al., eds. *Cutaneous Melanoma*. Philadelphia, PA: Lippincott; 1985, with permission.)

Sartorius Muscle Transposition . If the sartorius muscle is to be transposed, it is divided at its origin on the anterior superior iliac spine (Fig. 3.9). The lateral femoral cutaneous nerve is preserved if possible. The proximal neurovascular bundles going to the sartorius muscle are divided to facilitate transposition, with care to preserve others to the maximal extent possible to ensure a vascularized pedicle. The rotated

muscle is placed over the femoral vessels and tacked to the inguinal ligament, fascia of the adductor, and vastus muscle groups.

Wound Closure . The skin edges are examined for viability and trimmed back to healthy skin, if necessary. Intravenous administration of fluorescein followed by examination using a Wood lamp may be used to identify poorly perfused skin edges. Two closed-suction drains are generally placed through separate small incisions superiorly. One is laid medially and the other is laid laterally within the operative wound. The wound is closed with interrupted 3-0 undyed absorbable sutures in the dermis and followed by skin staples. In some patients, interrupted nylon sutures are used overlying the area of skin crease and running sutures used at both poles.

Postoperative Management . The patient begins ambulating the day following surgery; a custom-fit elastic stocking may be used during the day for 6 months. After this period, the stocking may be discontinued if no leg swelling occurs. Suction drainage is continued until output is less than 30 mL per day for 2 consecutive days. By approximately 3 to 4 weeks, the suction catheters are removed, regardless of the amount of drainage, to mitigate risk of infection.

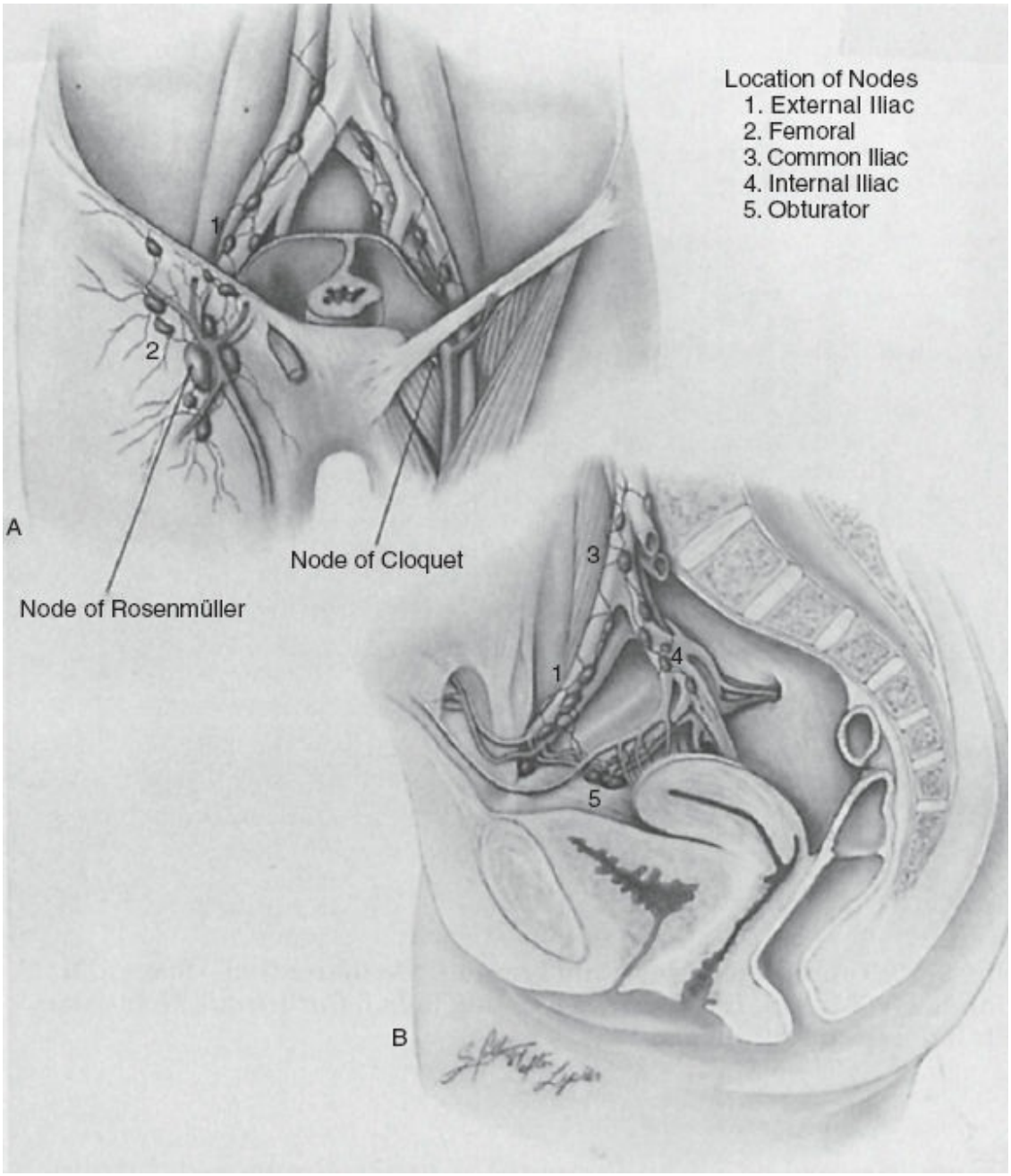


Figure 3.8 **A:** Lymphatic anatomy of the inguinal area demonstrating the superficial and deep lymphatic chains. Cloquet node lies at the transition between the superficial and deep inguinal nodes. It is located beneath the inguinal ligament in the femoral canal. **B:** The iliac nodes include those on the common and superficial iliac vessels and the obturator nodes. Obturator nodes should be excised as part of an iliac nodal dissection. (From Balch CM, Milton GW, Shaw HM, et al., eds. *Cutaneous Melanoma*. Philadelphia, PA: Lippincott; 1985, with permission.)

Dissection of the Iliac and Obturator Nodes

General . We generally perform deep dissection—dissection of the iliac and obturator nodes—for the following indications: (a) known involvement of the nodes revealed by preoperative imaging studies, (b) more than three grossly positive nodes in the superficial lymph node dissection specimen, or (c) metastatic disease in Cloquet node by frozen-section examination.

Incision . To gain access to the deep nodes, we extend the skin incision superiorly.

Lymph Node Dissection . The external oblique muscle is split from a point superomedial to the anterior superior iliac spine to the lateral border of the rectus sheath. The internal oblique and transversus abdominis muscles are divided, and the peritoneum is retracted superiorly. An alternative approach is to split the inguinal ligament vertically, medial to the femoral vein. The ureter is exposed as it courses over the iliac artery. Dissection continues in front of the external iliac artery to separate the external iliac nodes. The inferior epigastric artery and vein are divided, if necessary. Dissection of the lymph nodes continues to the bifurcation of the common iliac artery. Nodes in front of the external iliac vein are dissected to the point at which the internal iliac vein courses under the internal iliac artery. The plane of the peritoneum is traced along the wall of the bladder, and the fatty tissues and lymph nodes are dissected off the perivesical fat starting at the internal iliac artery. Dissection is completed on the medial wall of the external iliac vein, and the nodal chain is further separated from the pelvic fascia until the obturator nerve is seen. Obturator nodes are located in the space between the external iliac vein and the obturator nerve (in an anteroposterior direction) and between the internal iliac artery and the obturator foramen (in a cephalad–caudad direction). The obturator artery and vein usually need not be disturbed.

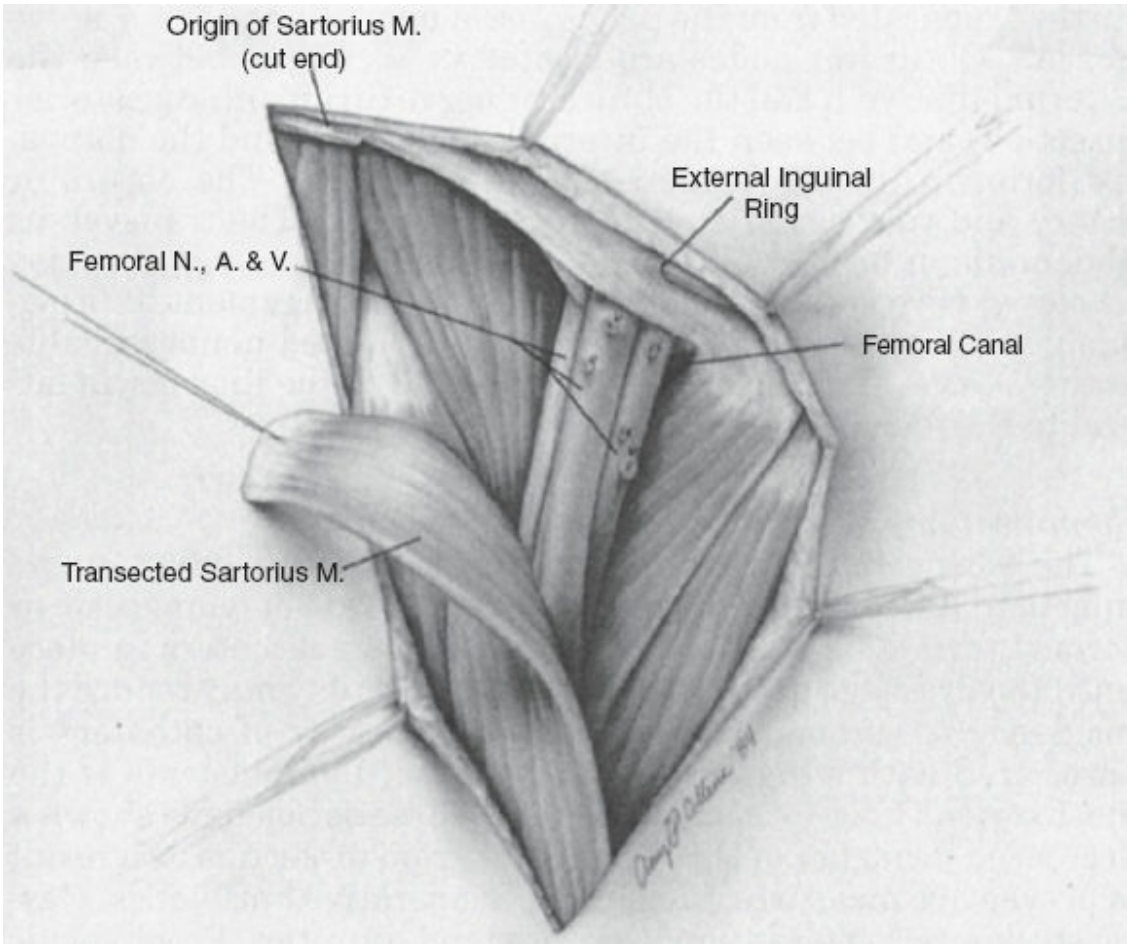


Figure 3.9 Transection of the sartorius muscle at its origin on the anterior superior iliac spine in preparation for transposition over the femoral vessels and nerves. (From Balch CM, Milton GW, Shaw HM, et al., eds. *Cutaneous Melanoma*. Philadelphia, PA: Lippincott; 1985, with permission.)

Wound Closure. The transversus abdominis, internal oblique, and external oblique muscles may be closed with running sutures. The inguinal ligament, if previously divided, is approximated with interrupted nonabsorbable sutures to Cooper ligament medially and to the iliac fascia lateral to the femoral vessels. A closed suction drain is placed in the deep pelvic space exiting through a separate small incision.

Postoperative Management. Suction drainage is continued until output is less than 30 mL per day for 2 consecutive days. The pelvic drain is usually removed prior to hospital discharge. Ambulation is encouraged the day after surgery. Patients are hospitalized postoperatively for expectant management of potential ileus after deep pelvic surgery and for pain control.

Neck Dissection

Lymph node metastases from melanomas in the head and neck were previously believed to follow a predictable pattern. However, it is now known that lymphatic drainage from melanomas of the head and neck can be multidirectional and unpredictable. ELND or SLNB may be misdirected in as many as 59% of patients if the operation is based on classic anatomical studies without preoperative lymphoscintigraphy. These findings strongly support the use of lymphoscintigraphy in patients with melanomas in the head and neck.

At MD Anderson, the treatment of choice for patients with melanoma in the head and neck region and clinically involved nodes is wide excision of the primary lesion with either modified radical neck dissection or selective neck dissection, followed by consideration of adjunctive radiation therapy.

Melanomas arising on the scalp or face anterior to the pinna of the ear and superior to the commissure of the lip can metastasize to intraparotid lymph nodes because these nodes are contiguous with the cervical nodes. When intraparotid nodes are clinically involved, it is advisable to combine neck dissection with parotid lymph node dissection and then administer adjuvant radiation therapy.

Morbidity of Lymph Node Surgery

Complications associated with SLNB for melanoma were evaluated in 2,120 patients in an analysis of data from the Sunbelt Melanoma Trial. Overall, 96 (4.6%) of the patients developed major or minor complications associated with SLNB, whereas 103 (23.3%) of 444 patients experienced complications associated with SLNB plus completion lymph node dissection. The authors concluded that SLNB alone is associated with significantly less morbidity compared to SLNB plus completion lymph node dissection. Similar to the Sunbelt Melanoma Trial, in MSLT-1, SLNB did not significantly add to the morbidity of melanoma surgery when compared to wide excision of the primary melanoma alone.

Formal lymphadenectomy is associated with higher complications rates, particularly in the inguinal region. Cormier et al. prospectively followed 53 patients at MD Anderson who underwent inguinal lymphadenectomy for melanoma; using liberal objective criteria, investigators found the acute wound complication rate to be 77.4% with a wound infection rate of 54.7% and a wound dehiscence rate of 52.8%. In multivariate analysis, only body mass index was found to be associated with an increase in

complications. The infection rate reported after lymphadenectomy in MSLT-1 was 12% and also noted that lymphedema varied significantly depending on the lymph nodes basins that were dissected (i.e., 9.0% for axillary lymphadenectomy vs. 26.6% for inguinal lymphadenectomy).

Lymphedema is among the most serious long-term complications of formal lymphadenectomy. Inguinal lymphadenectomy–associated lymphedema was not altered significantly by the addition of a deep groin dissection. In addition, the number of lymph nodes removed did not appear to alter the lymphedema rate significantly. In the study by Cormier et al., the lymphedema rate at 3 months was 85% using qualitative measures and 45% by quantitative measures for patients who underwent inguinal lymphadenectomy. Lower extremity edema after groin dissection can be decreased by preventive measures, including perioperative antibiotics, elastic stockings, leg elevation exercises, and diuretics. Even with preventive measures, patients should be counseled that lymphedema can still develop. Nonetheless, prophylactic measures are important because reversing the progression of lymphedema is difficult.

The complication rate for axillary lymph node dissections is lower than that for inguinal dissection. The most frequent complication is wound seroma, varying from 3% to 23%. Other common complications include cellulitis and lymphedema (approximately 10%). For all types of lymph node dissection, skin flap problems can occur. Expectant management of ischemic edges may result in full-thickness necrosis and prolonged hospitalization. Therefore, in the uncommon situation where skin flap edges are of questionable viability, the patient may be returned to the operating room early for flap revision.

Special Clinical Situations

Giant Congenital Nevi

A giant congenital nevus has been defined as a nevus that measures at least 15 cm in diameter or at least twice the size of the affected person’s palm. Patients with giant congenital nevi have an estimated 4% to 10% lifetime risk of developing a melanoma. Approximately half of melanomas that develop in giant congenital nevi develop within the first 5 years of life. Decisions about the management of giant congenital nevi are difficult because such lesions are often so extensive that prophylactic surgical excision is impossible. When the location and size of a lesion permit prophylactic excision, excision should be considered before the age of 2

years. Although data are limited, potential negative prognostic indicators that may aid in decision making include large size and the presence of satellite lesions.

Metastatic Melanoma of Unknown Primary Site

Approximately 1% to 8% of patients with melanoma present with metastatic disease from melanoma of unknown primary (MUP) site. The most common presentation is in the axillary lymph node basin (>50%). The next most common presentation site is the cervical lymph node basin. Various reasons have been proposed for the phenomenon of MUP site. Anbari et al. suggested the following possibilities for primary lesions: an unrecognized melanoma, a treated melanoma that had been initially misdiagnosed, a spontaneously regressed melanoma, and malignant transformation of a melanocyte that had travelled to a metastatic location. In order for metastatic melanoma to be classified as MUP site, the histologic diagnosis must be confirmed, previous biopsies and/or excisions, if any, should be evaluated for a possible diagnosis of melanoma, and less common primary sites for melanoma should be thoroughly evaluated. A thorough history may also identify prior lesion that was excised or destroyed, but never biopsied. If the metastatic lesion is to a lymph node basin, the drainage areas of that basin should be rigorously examined. Furthermore, patients should undergo staging evaluation with CT of the chest, abdomen, and pelvis (also including neck CT if anatomically appropriate), and MRI of the brain.

Several studies have compared the survival of these patients to similar cohorts having equivalent nodal status and a known primary site. Although patients with unknown primary tumors were historically believed to have worse prognoses, recent studies have contradicted earlier findings and by demonstrating that patients with MUP have a natural history that is similar to (if not better than) the survival of many patients with stage III disease. Given their survival profile, such patients with nodal disease should be staged as stage III and treated similar to stage III patients with a known primary melanoma, including consideration for stage III clinical trials.

MANAGEMENT OF LOCOREGIONAL NON-NODAL DISEASE

Background

The presence of clinically or microscopically detectable locoregional non-nodal disease can be broadly categorized into three groups:

1. In-transit metastases (classically defined as skin or subcutaneous metastases more than 2 cm from the primary lesion but not beyond the regional nodal basin).
2. Satellite metastases (classically defined as skin or subcutaneous lesions within 2 cm of the primary tumor).
3. Microsatellite disease (microscopic cutaneous and/or subcutaneous disease found adjacent to, but discontinuous from, the primary tumor not simply separated by fibrosis or inflammation).

Satellite/in-transit patterns of recurrence are relatively unique to melanoma and occur in 3% to 10% of melanoma cases. Although the molecular determinants and pathophysiology of in-transit disease are poorly understood, they are likely an intralymphatic manifestation of melanoma metastases. Independent predictors of in-transit recurrence among patients who underwent sentinel node biopsy include age older than 50 years, a lower-extremity primary tumor, increasing tumor thickness, ulceration, and nodal involvement. Regional nodal metastases occur in about two-thirds of patients with in-transit disease and, if present, are associated with lower survival rates. Other reported predictors of distant metastasis among patients with in-transit recurrence include positive SLN status, in-transit tumor size of at least 2 cm, and disease-free interval before in-transit recurrence of less than 12 months. Data suggest that patients who present with synchronous, distant, and in-transit disease have a worse disease-specific survival compared to patients who present with only in-transit or distant disease.

Historically, some have suggested that dissection of the regional nodal basin—by either SLNB (see section below) or complete lymphadenectomy—increases the risk of in-transit metastases. These authors hypothesized that dissection disturbs lymph flow, leading to deposition of metastatic cells in the intervening lymphatic vessels. A critical analysis of the data, however, provided compelling evidence that neither SLNB nor completion lymph node dissection in SLN-positive patients increases the incidence of in-transit metastases. In a collaborative review by MD Anderson and the Sydney Melanoma Unit of 3,400 patients with primary melanomas at least 1 mm thick treated over a 10-year period at the Sydney Melanoma Unit, there was no significant difference in the rate of in-transit metastases between patients treated with wide excision alone (4.9%) and those treated

with wide excision and SLNB (4.5%). Because the two groups were similar in terms of median tumor depth, fraction with ulcerated tumors, and Clark level, these data strongly support the concept that early nodal intervention has little impact on the natural history of in-transit metastases. In a separate study of 1,395 patients from The University of Texas MD Anderson Cancer Center, patients with a positive SLN had a significantly higher rate of in-transit metastases (12%) than patients with a negative SLN (3.5%). Taken together, these data indicate that biology—not surgical technique—establishes the risk of in-transit metastases.

Approach to Treatment

Treatment options for patients with locoregional non-nodal disease include surgery, regional approaches, and systemic therapy. Patients with in-transit metastases confined to a limb that are not amenable to standard surgical measures (e.g., patients with recurrent and/or multiple in-transit metastases and patients with large-burden in-transit disease) pose a unique treatment challenge. Locoregional options include regional chemotherapy techniques such as isolated limb perfusion or isolated limb infusion, or intralesional therapy. Amputation is rarely indicated.

Hyperthermic Isolated Limb Perfusion

Hyperthermic isolated limb perfusion (HILP) with melphalan has been used to treat in-transit metastases of the extremities since the mid-1950s. With this procedure, a formal lymph node dissection is performed which provides exposure to the critical vessels of interest. Subsequently, cannulae are inserted and the extremity is placed on an extracorporeal (oxygenated) bypass circuit after a tourniquet is applied, effectively isolating the limb from systemic circulation. Melphalan is currently the most active single agent for use in HILP. Overall response rates of 64% to 100% (median complete response rates of 58%) can be achieved, and the median response duration in patients with a complete response ranges from 9 to 19 months. Nonrandomized studies of hyperthermic limb perfusion by Lienard et al. reported a high complete response rate (90%) with a combination of melphalan, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), and a somewhat lower response rate with melphalan alone (52%). Fraker et al. reported a 100% response rate in patients treated with melphalan alone and a 90% response rate in patients treated with

melphalan, IFN-γ, and TNF-α, although the latter combination resulted in a higher complete response rate (80% vs. 61%). A multicenter randomized trial sponsored by the American College of Surgeons Oncology Group comparing melphalan alone with a combination of melphalan and TNF-α for patients who have in-transit metastases was closed to accrual early because an interim analysis failed to reveal a benefit for TNF-α. Thus, TNF-α is not available in the United States for isolated limb perfusion procedures.

The routine use of HILP in the adjuvant setting has marginal, if any, benefit. Although a randomized multicenter phase III trial of 86 patients (Hafstrom et al.) showed increased disease-free interval in patients with in-transit metastases and regional lymph node metastasis, this effect was transient and predominantly occurred in patients with a more favorable prognosis (tumor thickness of 1.5 to 2.99 mm). This study showed no benefit of isolated limb perfusion with respect to time to distant metastasis or survival duration.

Although HILP may be an effective treatment option for patents with in-transit metastases, the technique is complex and invasive. To address these challenges, the technique of minimally invasive of isolated limb infusion was developed.

Isolated Limb Infusion

Isolated limb infusion is essentially a low-flow minimally invasive isolated limb perfusion performed via percutaneously inserted catheters, but without oxygenation of the circuit (Fig. 3.10). Using standard radiologic techniques, catheters are inserted percutaneously into the main artery and vein of the unaffected limb (or they can be placed in the main artery and vein in the affected limb, i.e., brachial or popliteal artery and vein). Under general anesthesia, after a pneumatic tourniquet is inflated proximally, cytotoxic agents (generally melphalan and actinomycin-D) are infused through the arterial catheter and “hand-circulated” with a syringe technique for 20 to 30 minutes. Progressive hypoxia occurs because, in contrast to isolated limb perfusion, no oxygenator is used. The hypoxia and acidosis associated with isolated limb infusion are therapeutically attractive because numerous cytotoxic agents, including melphalan, appear to damage tumor cells more effectively under hypoxic conditions; hypoxia and acidosis have been reported to increase the cytotoxic effects of melphalan in experimental models.

At the completion of the drug exposure, the limb vasculature is flushed with a crystalloid solution via the arterial catheter, and the effluent is discarded. Although the limb tissues are exposed to the cytotoxic agent for only a short period (up to 30 minutes), the procedure has been shown to yield response rates roughly similar to those observed after conventional HILP; overall response rates of 85% (complete response rate, 41%; partial response rate, 44%) have been achieved in at least one study. A multi-institutional study by Beasley et al. revealed a 31% complete response rate and a 33% partial response rate. Because of the relatively simplicity of the isolated infusion technique, it may be a more attractive option for patients with prohibitive comorbidities or the elderly, and in general is more widely used than HILP.

Toxicity and Morbidity of HILP and Isolated Limb Infusion

HILP and isolated limb infusion can be associated with potentially significant regional adverse effects, including myonecrosis, nerve injury, compartment syndrome, and arterial thrombosis, sometimes necessitating fasciotomy or rarely amputation. Following isolated limb infusion, regional adverse events appear to be similar to those reported after conventional HILP, with 41% of patients experiencing grade II toxic effects and 53% experiencing grade III toxic effects. Systemic toxicity, including hypotension and adult respiratory distress syndrome, has sometimes been seen with the addition of TNF-α to the perfusion or infusion regimen. To avoid renal injury secondary to high creatine phosphokinase levels, the rate of fluid resuscitation may need to be increased and alkalinizing the urine has theoretical benefits. Steroids have been used empirically to reduce the amount of muscle injury. Of note, the peak creatine phosphokinase level is generally on postoperative day 1 for isolated limb perfusion and day 4 for isolated limb infusion. Because both limb perfusion and infusion require a high degree of technical expertise and are associated with a significant risk of complications, the procedures should be performed only in centers that have experience with the technique. At present, there is little evidence to justify the use of prophylactic perfusion or infusion, except as part of a clinical trial.

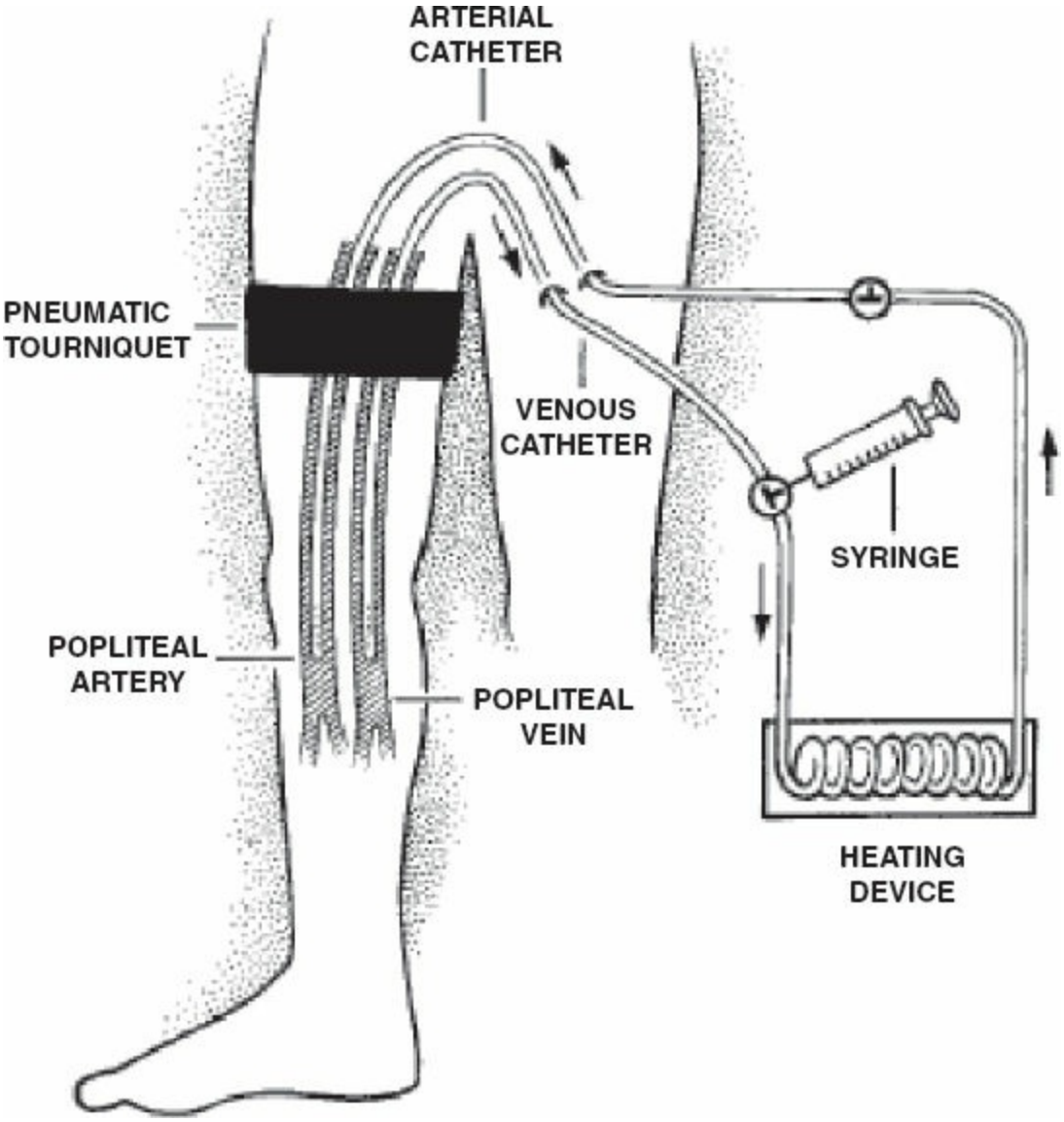


Figure 3.10 Schematic drawing depicting an isolated limb infusion. The catheters are typically placed percutaneously by an interventional radiologist via the contralateral extremity, with the catheter tips positioned in the tumor-bearing extremity just below the inguinal ligament in the superficial femoral artery and vein. After inflation of the tourniquet, chemotherapy is manually infused for 20 to 30 minutes, after which the limb is washed out with normal saline. (Reprinted from Lindner P, Doubrovsky A, Kam PC, et al. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann Surg Oncol* 2002;9:127–136, with permission.)

Intralesional Therapy

The concept of intralesional therapy for locoregional in-transit disease (or more broadly speaking for other accessible metastases) in melanoma is not

new; recently, some of these agents have shown promising results. A potential advantage of such a strategy is that a direct targeted approach may be associated with limited systemic toxicity while at the same time promoting a favorable local immune response. Historically, this approach has been considered for patients with unresectable, multiple, or locally advanced stage IIIB and IIIC disease as well as patients with accessible M1a disease.

One of the first agents employed was Bacillus Calmette-Guérin (BCG) in the mid-late 20th century. Early reports by Morton et al. revealed not only significant tumor regression in a majority of injected lesions but also the induction of a host antitumor activity in regional and distant uninjected sites, despite lack of any real visceral response. As the use of intralesional BCG became more widespread, some significant toxicities were reported including severe allergic reactions and anaphylaxis and death due to disseminated BCG. Although several nonrandomized trials using historical controls and two small randomized trials of intralesional or intralymphatic BCG showed a statistically significant OS benefit in favor of BCG, randomized trials failed to substantiate these findings.

Multiple intralesional agents have been investigated, many of which are currently in clinical trials.

PV-10 is a sterile, nonpyrogenic solution of 10% Rose Bengal disodium, a fluorescein derivative. Intralesional injection of PV-10 leads to intratumoral necrosis and locoregional inflammation that facilitate the generation of neoantigenic tumor fragments and their presentation to antigen presenting cells. A phase II study performed by Melanoma Institute Australia showed an overall response rate of 51% for target lesions and a complete response rate of 26%. Median time to response was 1.9 months, median duration of response was 4.0 months, and 8% of patients were without evidence of disease after 52 weeks.

The T-VEC (talimogene laherparepvec) intralesional strategy leverages the role of granulocyte macrophage colony stimulating (GM-CSF) injection and its theoretical contribution to antitumor immunity. The agent is an attenuated oncolytic herpes simplex virus that has been modified to express the GM-CSF gene, and is also capable of selective replication in tumor cells. The antitumor effect is thought to be due to a combination of a direct oncolysis from the viral infection and lytic replication, as well as the induction of a systemic immune response.

In a phase III trial reported by Andtbacka et al., 436 patients were

enrolled and randomized to T-VEC or GM-CSF (control). All patients had unresectable, injectable stage III or IV melanoma with a limited visceral disease burden. T-VEC was administered by intralesional injections once every 2 weeks, while in the other arm GM-CSF was administered subcutaneously daily for 14 days in each 28-day cycle. The durable (defined as ≥6 months) response rate, the primary objective of the trial, was significantly increased in patients receiving T-VEC (16.3% vs. 2.1%), as was the overall response rate (26.4% vs. 5.7%). Some antitumor effects were observed in approximately 1/3 of uninjected lesions and in slightly more than 10% of visceral sites. Overall survival (OS) was not significantly different among the arms of the trial in general; however, in subset analysis there appeared to be a survival advantage in patients with stage III or IV (M1a) disease (4-year OS 32% vs. 21%, HR 0.57, 95% CI 0.40 to 0.80). Treatment with T-VEC was well tolerated; commonly reported adverse events included fatigue, chills, pyrexia, and other systemic flu-like symptoms. Based on these positive clinical results, in 2015, T-VEC became the first intralesional therapy approved by the FDA for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Recent efforts have attempted to build upon the success of ILI and intralesional therapy (T-VEC in particular) in keeping with the momentum from combinatorial strategies. Ariyan et al. examined the safety and efficacy of combining ipilimumab with ILI in patients with in-transit disease. Their initial reports suggest this is a safe and efficacious combination, with response rates of 89% at 3 months (65% CR) and progression-free survival (PFS) at 1 year of 57%. Only 18 patients were enrolled and what remains to be seen is whether these results augment either response or durability of ILI monotherapy with continued accrual and follow-up. T-VEC–based combinatorial trials are also ongoing, in combination with ipilimumab and other immune checkpoint inhibitors, and in earlier stages of disease (i.e., neoadjuvant).

ADJUVANT THERAPY FOR LOCOREGIONAL DISEASE

Interferon Alfa-2b

High-dose IFN alfa-2b has been approved by the U.S. FDA as adjuvant treatment for patients with melanoma who have a high risk of recurrence for the past two decades. Patients with locally advanced, recurrent, nodal,

in-transit, or satellite disease have been considered candidates for adjuvant high-dose IFN alfa-2b.

Approval of IFN alfa-2b was based on the results of the Eastern Cooperative Oncology Group (ECOG) E1684 prospective randomized trial, which assigned 287 patients to high-dose IFN alfa-2b or observation after wide excision. The IFN alfa-2b dosage was 20 million units/m^2/day intravenously for 4 weeks followed by 10 million units/m^2 three times a week subcutaneously for the next 48 weeks. Both node-positive and high-risk node-negative (T4pN0) patients were included; most patients had recurred in the regional nodes after prior wide excision. All patients underwent either ELND or TLND. Of the 287 patients enrolled, 89% were node positive. IFN alfa-2b improved median OS from 2.8 to 3.8 years and 5-year relapse-free survival (RFS) rates from 26% to 37% at a median follow-up of 7 years. The beneficial effect of IFN alfa-2b was most pronounced in the node-positive patients. Of note, the rate of toxic effects was high: Two patients died, 67% of patients experienced grade 3 toxic effects, and 50% of patients either stopped treatment early or required dose reduction.

An updated analysis of E1684, at a median follow-up of 12.6 years, showed a persistent gain in median disease-free survival (45.8 months for the IFN alfa-2b arm vs. 32 months for observation). The OS difference, however, was no longer statistically significant, possibly because deaths from intercurrent illness on both arms overshadowed melanoma-specific mortality.

The E1690 trial, another ECOG trial, was initiated before a significant impact on survival had been noted in E1684. In E1690, designed as a confirmation and extension of E1684, 642 patients with high-risk (stage IIB or III) melanoma were randomized in a three-arm study to receive the E1684 high-dose regimen, low-dose IFN alfa-2b (3 million units/m^2 three times a week for 2 years), or observation only. Seventy-five percent of the patients had nodal metastases (50% had recurrent disease in the regional nodes). Unlike E1684, E1690 allowed entry of patients with T4 primary tumors, regardless of whether lymph node dissection was performed, and 25% of the patients in the trial had deep primary tumors (compared to 11% in E1684).

In E1690, at a median follow-up of 52 months, high-dose IFN alfa-2b demonstrated an RFS benefit exceeding that of low-dose IFN alfa-2b or observation. The 5-year estimated RFS rates for high-dose IFN alfa-2b,

low-dose IFN alfa-2b, and observation were 44%, 40%, and 35%, respectively ($P = 0.03$). The RFS benefit was equivalent for node-negative and node-positive patients. Neither high-dose nor low-dose IFN alfa-2b demonstrated an OS benefit compared to observation.

An analysis of salvage therapy for patients whose disease relapsed on E1690 demonstrated that a significantly larger proportion of patients in the observation arm than in the high-dose IFN arm received IFN alfa-containing salvage therapy, which may have confounded interpretation of the survival benefit of assigned treatments. Some of the discrepancy between the findings of E1684 and E1690 may be attributable to differences in patient demographic profiles. E1690 included patients with more favorable disease characteristics: only 75% of patients were node positive, and of these, 51% had nodal recurrence. In E1690, 25% of patients enrolled were clinical stage II; in E1684, 11% were pathologic stage II. Presumably, some of the clinical stage II patients in E1690 would have been pathologic stage III had lymphadenectomy been required. An updated analysis of E1690 with a median follow-up of 7.2 years has confirmed the study's original conclusions. Furthermore, pooled analysis of ECOG 1684 and ECOG 1690, demonstrated that high-dose IFN led to improved disease-free survival versus placebo, but there remained no benefit with regards to OS.

ECOG trial E1694 was initiated to compare the efficacy and safety of a ganglioside vaccine with the efficacy and safety of high-dose IFN alfa-2b in patients with stage IIB or stage III melanoma. The ganglioside GM2 is a serologically well-defined melanoma antigen and immunogenic ganglioside expressed on melanoma cells. Preliminary studies had suggested that the antibody response to GM2 was correlated with relapse-free and OS. In E1694, 774 eligible patients with high-risk melanoma (tumor thickness >4 mm or regional lymph node metastasis) were randomized to receive high-dose IFN alfa-2b or GM2 vaccine. The study was closed early by the data safety monitoring board because of the clear superiority of IFN alfa-2b in terms of both disease-free and OS. The estimated 2-year RFS rates were 62% in the high-dose IFN alfa-2b arm and 49% in the GM2 vaccine arm. Furthermore, analysis of the hazard of relapse and death in subgroups based on the number of lymph nodes demonstrated the superiority of IFN alfa-2b over GM2 in all nodal subsets. E1694 also showed a statistically significant benefit for IFN alfa-2b in node-negative high-risk patients.

A pooled meta-analysis of primary data from the ECOG/Intergroup trials of high-dose IFN (N = 1,916) revealed a clear benefit of high-dose IFN alfa-2b in terms of RFS and a more modest benefit in terms of OS (odds ratio = 0.9, P = 0.05). Data from an updated analysis of the ECOG database demonstrated that (a) the survival impact of IFN alfa-2b was confined to regimens that incorporated both high-dose induction and high-dose subcutaneous maintenance; (b) reduction of hazard was observed early; and (c) the RFS advantage was sustained off treatment, in contrast to the more limited RFS advantage reported by the low-dose trials.

Results of trials investigating low-dose IFN alfa-2b have been disappointing. The previously mentioned E1690 trial, a three-arm trial that included low-dose IFN alfa-2b as one of the treatments, demonstrated no significant improvement in RFS in patients with high-risk stage II or stage III melanoma who received low-dose IFN alfa-2b for 2 years. The modest improvement in the low-dose IFN alfa-2b arm compared to the control arm disappeared within 2 years after therapy was stopped. The European Organization for Research and Treatment of Cancer (EORTC) 18871 trial also demonstrated that very low-dose IFN alfa-2b (1 million units per m^2) injected subcutaneously on alternate days for 1 year did not affect OS for patients with high-risk melanoma. Because of the lack of a demonstrable durable clinical benefit, low-dose IFN alfa-2b has not been approved as adjuvant therapy for melanoma in the United States. Similarly, intermediate dose interferon was studied with EORTC 18952. No disease-free or OS benefits were demonstrated.

In March 2011, the FDA approved PEG-IFN alfa-2b for the adjuvant treatment of melanoma with microscopic or gross nodal involvement. The treatment is to be started within 84 days of definitive surgical resection including complete lymphadenectomy, and is dosed as a once-weekly subcutaneous injection that may be self-injected. The recommended dose is 6 μg/kg/wk subcutaneously for 8 doses, followed by 3 μg/kg/wk subcutaneously for up to 5 years. Approval was based on EORTC 18991, an open label, multicenter trial that enrolled 1,256 patients. Patients who had adequate surgical resection of their primary cutaneous melanoma and affected regional lymph nodes were randomized to receive either PEG-IFN alfa-2b or observation for a 5-year period. Stratification factors included type of nodal involvement (microscopic vs. gross), number of positive nodes (1, 2 to 4, 5 or more, or not assessed), Breslow primary thickness (<1.5 mm, ≥1.5 to 4 mm, ≥4 mm), ulceration of primary tumor (present or

absent or unknown), sex, and study center. Patients were assessed for local and regional recurrence or distant metastases every 3 months for the first 2 years of treatment and subsequently every 6 months through the end of the trial. Improved RFS was seen in the PEG-IFN alfa-2b cohort compared to the observation group (hazard ratio 0.82 [95% CI: 0.71, 0.96]; unstratified log-rank $P = 0.011$). The estimated median RFS was 34.8 months (95% CI: 26.1, 47.4) and 25.5 months (95% CI: 19.6, 30.8) in the PEG-IFN alfa-2b and observation arms, respectively. However, there was no difference in OS seen between the two groups (hazard ratio 0.98 [95% CI: 0.82, 1.16]). A total of 33% of patients receiving PEG-IFN alfa-2b discontinued treatment due to adverse reactions. The most common adverse reactions present at the time of treatment discontinuation were fatigue, depression, anorexia, increased ALT, increased AST, myalgia, nausea, headache, and pyrexia.

Immune Checkpoint Blockade

The use of immune checkpoint blockade via monoclonal antibodies targeting anti-CTLA4 (ipilimumab; *Yervoy*) has been established as an effective treatment for stage IV disease since 2011. However, its use in the adjuvant setting is a more recent clinical consideration. Although approved in 2015 for use in the adjuvant setting based on results from EORTC 18071, there is still much debate among practitioners regarding the cost versus benefit of this regimen.

A large randomized phase III trial (EORTC 18071) comparing high dose ipilimumab to placebo in 951 patients showed a significant decrease in the rate of recurrence (5-year RFS 40.8% vs. 30.3%, hazard ratio [HR] 0.76, 95% CI 0.64 to 0.89) and improved OS (5-year OS 65.4% vs. 54.4%, HR 0.72, 95% CI 0.58 to 0.88, $P = 0.001$) and was largely responsible for its subsequent approval in this setting. Ipilimumab was administered at a dose of 10 mg/kg every 3 weeks for four doses, then every 3 months for 3 years unless toxicity or relapse prevented its continuation. Placebo was administered on the same schedule.

Despite the survival benefits noted in this adjuvant setting, opponents of this approach remark on the toxicity, paradoxical increased dosing seen in the adjuvant setting compared to metastatic disease (the latter of which employs a dose of 3 mg/kg every 3 weeks × four doses), and the lack of a head to head comparison to interferon. The toxicity from the EORTC 18071 trial was not trivial; adverse events of any grade were noted in

98.7% of patients treated with ipilimumab, including 54.1% with grade 3 or 4. The median number of ipilimumab doses was four. Furthermore, there were five treatment-related deaths in patients treated with ipilimumab (three due to colitis, one to myocarditis, and one to multiorgan failure associated with Guillain–Barré syndrome). While treatment-related deaths may be encountered in any clinical trial, such events in the adjuvant setting raise caution; some argue whether the toxicity is worth the potential survival benefit. This is relevant since there is a fraction of patients who will never recur and therefore have no potential to benefit from any adjuvant therapy; of course, the challenge is that it is currently not possible to know at the level of an individual patient. Therefore, the ability to prospectively identify *higher and lower* risk patients with biomarkers is an area of ongoing interest.

Another ongoing randomized phase III clinical trial in the adjuvant setting (AJCC 7th edition stages IIIB, IIIC, or IV melanoma) compares ipilimumab at one of two dose levels (i.e., 10 mg/kg dose used in EORTC 18071 or the standard 3 mg/kg dose approved for patients with unresectable/metastatic disease) with high-dose IFN alfa-2b (ECOG E1609, NCT01274338). Co-primary endpoints include OS and relapse-free survival (RFS). Interim results have shown significantly more toxicity associated with the 10 mg/kg dose versus 3 mg/kg. An unplanned RFS analysis of concurrently randomized patients on the 2 ipilimumab arms showed no difference in RFS at median follow-up of 3.1 years.

More recently, the PD-1 axis of checkpoint blockade was explored in the adjuvant setting using the anti–PD-1 monoclonal antibody nivolumab. In patients with stage IV melanoma, treatment with nivolumab has been associated with a more favorable toxicity profile and improved response rates when compared with ipilimumab. In a randomized, double-blind, phase 3 clinical trial (CheckMate 238) for patients with resected advanced melanoma, over 900 patients who underwent complete resection of stage IIIB, IIIC, or IV melanoma received either nivolumab (3 mg/kg every 2 weeks) or ipilimumab (10 mg/kg every 3 weeks × 4 doses and then every 12 weeks). At a minimum follow-up of 18 months, the 12-month RFS was 70.5% (95% confidence interval [CI], 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group (hazard ratio [HR] for disease recurrence or death, 0.65; 97.56% CI, 0.51 to 0.83; $P < 0.001$). Toxicity (grade 3 or 4 adverse events) were reported in 14.4% of the patients in the nivolumab group versus 45.9% of patients in the

ipilimumab group; moreover, two deaths (0.4%) were reported and noted to be related to toxic effects in the ipilimumab group. Weber et al. concluded that nivolumab resulted in significantly longer RFS and a lower rate of grade 3 or 4 adverse events than adjuvant therapy with ipilimumab. It is anticipated that nivolumab will be FDA approved in the adjuvant setting in the near future.

Targeted Therapy

Targeted BRAF and MEK dual inhibition (BRAFi/MEKi) in $BRAF^{V600}$ mutant melanoma has been associated with relatively rapid response, high disease control rates, and a survival benefit in stage IV melanoma. Unfortunately, this approach has also been associated with limited durability of response, leading some investigators to examine alternate stages of disease for this regimen. Long et al. investigated the efficacy of these agents in the adjuvant stage III setting in a recently published randomized, double-blind, placebo-controlled, phase 3 trial (COMBI-AD), that randomly assigned patients with completely resected stage III melanoma and $BRAF^{V600}$ mutations (N = 870) to receive oral dabrafenib (150 mg BID) plus trametinib (2 mg once daily) versus placebo in a 1:1 fashion. At a median follow-up of 2.8 years, the estimated 3-year RFS was 58% in the combination-therapy group and 39% in the placebo group (HR for relapse or death, 0.47; 95% CI, 0.39 to 0.58; $P < 0.001$). In addition, the BRAFi/MEKi group had a significantly higher 3-year OS of 86% versus 77% in the placebo group (HR for death, 0.57; 95% CI, 0.42 to 0.79; $P = 0.0006$); authors noted that this level of improvement did not cross the prespecified interim analysis boundary of $P = 0.000019$. They concluded that combined dabrafenib plus trametinib in the adjuvant setting resulted in a significantly lower risk of recurrence in patients with stage III melanoma with $BRAF^{V600}$ mutations and with an acceptable toxicity profile.

Chemotherapy

No studies have demonstrated a benefit of adjuvant chemotherapy in patients with melanoma who are at high risk for relapse. On the contrary, a randomized trial of adjuvant dacarbazine versus no treatment showed a statistically significant decrease in survival in the adjuvant treatment arm. Adjuvant chemotherapy should be considered only in the context of a

clinical trial.

MANAGEMENT OF LOCAL RECURRENCE

True local recurrence is defined as recurrence at the site of the primary tumor, within or continuous with the scar, and is most likely the result of incomplete excision of the primary tumor; it represents a relatively rare pattern of recurrence. In many cases, such “local recurrences” may more appropriately be considered persistence of the primary tumor. A local recurrence consisting of a single lesion in a patient whose primary melanoma had favorable prognostic features may be appropriately treated with wide excision similar to a primary melanoma lesion. Patients with local recurrences consisting of multiple, small, and superficial lesions may be treated in a fashion similar to that used to treat patients with in-transit disease (see above).

MANAGEMENT OF DISTANT METASTATIC DISEASE

Common sites of distant metastasis in melanoma patients are, in order of decreasing frequency, skin and subcutaneous tissues (40%), lungs (12% to 36%), liver, and brain. Historically, patients with systemic metastases have had a poor prognosis, with a median survival ranging from 6 to 12 months. However, in the wake of effective and durable systemic therapies (see sections on Immunotherapy and Targeted Therapy), general guidelines for choosing treatment modalities continue to evolve. Although distant metastatic disease continues to portend a poorer prognosis, there have been marked improvements in survival rates for this cohort over the last decade. The combination of certain immune checkpoint inhibitors (ipilimumab and nivolumab) were shown to initially increase 1-year survival to approximately 85% from 30% to 35% in 1990. This trend continues to be improved upon with 2-year and even 5-year survival rates of 63.8% and 34%, respectively, in certain populations of patients treated with various immunotherapy regimens. In certain ways, some patients with stage IV disease are being treated as those with chronic versus terminal disease. Depending on performance and disease status, treatment plans have become centered on the “next best” approach in this realm. With that in mind, the practitioner and patient now have a variety of treatment options to employ as needed. These include surgical metastasectomy (curative or palliative), systemic immune and/or targeted therapy, occasional use of

conventional chemotherapy, intralesional therapy, combinational strategies, as well as exploration of new agents and approaches. Clinical trials therefore constitute a robust and important option for many patients in whom distant metastases are diagnosed as clinicians continue outcomes for patients with advanced melanoma.

Surgery

Complete metastasectomy may be considered in patients in whom it is an option as part of a multidisciplinary approach to the patient with distant metastasis. In stage IV patients who underwent complete metastasectomy as part of an adjuvant stage IV clinical trial (Canvaxin phase III trial), 5-year survival was a remarkable 40%. Several nonrandomized trials have demonstrated similar results after complete resection of all evident metastases. Patient selection is critical for the strategy of complete surgical metastasectomy. Of more than 4,229 patients at John Wayne Cancer Center with stage IV melanoma, 33.6% underwent surgical resection. The 5-year OS for this group was 16%, versus 7% for those who did not undergo resection. To aid in patient selection, a thorough imaging evaluation is suggested, including MRI of the brain and CT or PET/CT of the chest, abdomen, and pelvis. Patient factors also play a role in selection. Patients should not have comorbidities that would preclude a possible full recovery from surgery within 4 to 8 weeks so as to allow for the initiation of adjuvant or systemic therapies. Finally, the biology of the malignancy itself should be considered: patients whose distant metastasis developed following a longer disease-free interval or who present with isolated or oligometastatic disease are, in general, more likely to be considered for surgical resection.

Surgery may also offer effective palliation for isolated or oligometastatic accessible distant metastases. Examples of accessible lesions include isolated visceral metastases, isolated brain metastases, and occasionally isolated lung metastases. Palliative strategies may improve functional status and render patients more likely to tolerate systemic treatments.

Lesions Causing Gastrointestinal Tract Obstruction

Gastrointestinal tract obstruction from metastatic melanoma is usually due to lesions that mechanically obstruct the bowel or act as a lead point for intussusceptions. These submucosal lesions are generally removed by

bowel resection. Patients should also be prepared for the possibility of an ileostomy or colostomy.

Pulmonary Metastases

After subcutaneous metastases, the lungs are the next most common site of distant melanoma metastases. The 1-year survival in these patients has been reported to be about 50%. The value of pulmonary resection for melanoma metastases is controversial. In a study examining 65 pulmonary resections performed for histologically proven pulmonary metastases discovered after treatment of the primary melanoma, the post-thoracotomy actuarial survival rate was 25% at 5 years (median interval from pulmonary resection to death, 18 months). Patients without regional nodal metastases before thoracotomy had a median survival of 30 months, compared to 16 months for all other patients. The authors concluded that patients with isolated pulmonary metastases from melanoma may benefit from resection of those metastases. However, many patients with stage IV disease are not resectable at the time of stage IV diagnosis. A study of patients who presented with melanoma pulmonary metastasis found that only 21% were resectable at diagnosis. A retrospective evaluation of the International Registry of Lung Metastases, however, found that melanoma patients who underwent complete pulmonary metastasectomy had a 5-year survival rate of 22%.

Liver Metastases

Approximately 15% to 20% of patients with distant metastatic melanoma have liver metastases. Historically, the median survival of patients with liver metastases has ranged from 2 to 7 months. Some investigators have suggested that resection of hepatic metastasis is not warranted because of the associated dismal prognosis. Other investigators have suggested that resection may be appropriate only in patients with an ocular primary tumor because their clinical course is better than that of patients with liver metastases from cutaneous primary tumors. In a retrospective multicenter series of 40 patients who underwent resection of liver metastases from melanoma, 75% of the patients developed a subsequent recurrence. Patients with cutaneous melanoma were significantly more likely to have a subsequent recurrence outside the liver, suggesting that the disease is systemic at the time of hepatic resection. No patient with cutaneous melanoma metastatic to the liver was alive at 5 years. Thus, selection of

patients for resection of hepatic metastases must be individualized and include an extensive evaluation of the extent of the disease. In a study from the John Wayne Cancer Institute and the Sydney Melanoma Unit (*N* = 1,750 melanoma patients with hepatic disease), only 2% were candidates for hepatic resection. The 5-year survival in the resected group (complete or incomplete) was 29% versus 4% for those who did not undergo surgery. Similarly, a multi-institutional study that included MD Anderson Cancer Center, Duke University Medical Center, and centers in France and Italy revealed a median survival of 23.6 months in these highly selected patients who underwent resection. As with other sites of metastases, resection should be considered only as part of a multidisciplinary team approach.

Brain Metastases

Melanoma ranks behind only small-cell carcinoma of the lung as the most common tumor that metastasizes to the brain. An unusual feature of brain metastases is their propensity for hemorrhage, which occurs much more frequently with melanoma than other primary tumors. Hemorrhage occurs in 33% to 50% of patients with brain metastases from melanoma. Prognosis worsens with an increasing number of lesions and the presence of neurologic symptoms; median survival has historically been reported to be 3 to 4 months.

Surgical excision (followed in selected cases by cranial irradiation) is generally the treatment of choice in the case of a solitary, surgically accessible brain metastasis. Tumor excision is relatively safe, alleviates symptoms in most patients, and prevents further neurologic damage. Although long-term disease-free survival is uncommon, a rare patient may live more than 5 years after surgery. Radiation therapy is preferred when the lesions are numerous or are located in areas that preclude a safe operation. Stereotactic radiosurgery is also an important option for patients with small to medium brain metastases who have a reasonable life expectancy and no signs of increased intracranial pressure. For patients with multiple metastases that are not amenable to resection, whole brain radiation may assist in slowing the growth of metastases, although its use is controversial in some clinical circles.

Recurrent Distant Metastases

Unfortunately, many patients undergoing complete surgical resection of distant metastatic melanoma (stage IV) develop recurrent disease. In a

study conducted prior to the recent wave of FDA-approved systemic therapies for advanced melanoma, investigators examined whether a second metastasectomy could prolong the survival of patients with recurrent stage IV melanoma. In this study, the recurrent disease affected soft tissue, pulmonary, gastrointestinal, cerebral, skeletal, and gynecologic sites. Median survival following treatment for recurrent stage IV melanoma was 18.2 months after complete metastasectomy, compared to 12.5 months after a palliative surgical procedure and 5.9 months after nonsurgical management. The 5-year survival rate was 20% for patients in the complete metastasectomy group, compared to 7% for those in the palliative surgery group and 2% for those in the nonsurgical group. By multivariate analysis, the two most important prognostic factors for survival following diagnosis of recurrent stage IV melanoma were a prolonged disease-free interval before recurrence and complete surgical removal of the recurrent disease. These findings indicate that in a very highly select patient population, metastasectomy can prolong the survival of patients with recurrent stage IV melanoma and may be considered in the context of multidisciplinary team management if all clinically evident tumors can be resected.

Targeted Therapy

Targeted therapy exploits the concept of specificity in the realm of cancer treatment. These include kinase inhibitors that act upon a specific molecular target(s) thereby disrupting cellular proliferation pathways involved in tumor development and proliferation. Following an established track record set by other malignancies, such as breast cancer (trastuzumab) and leukemia/GIST (imatinib), melanoma is in the midst of a paradigm change in cancer treatment. Of note, to date, all targeted therapy agents used to treat melanoma have the advantage of being able to be administered orally. Given the ease of administration and the often profound disease control seen with these agents (see below), it is our practice at MD Anderson to routinely molecularly characterize tumors of patients with metastatic disease so that targeted therapy treatment options can be integrated into an overall treatment strategy.

BRAF Inhibitors

Over the past decade, attention has turned to leveraging our improved understanding of the underlying molecular biology of melanoma by using

such information to develop potential pathway-specific targeted therapeutics as a potential treatment for patients with metastatic melanoma. An important example of this approach is the development of novel therapeutics that target mutant BRAF (V600E) in metastatic melanoma. The BRAF gene encodes for production of B-RAF, a protein involved in cell signaling and growth. BRAF mutations have been found in approximately 50% of invasive cutaneous melanomas. BRIM-3 is a randomized, open-label, multicenter, phase III study that compared a BRAF inhibitor, PLX4032 (vemurafenib), to dacarbazine for treatment of previously untreated, unresectable, stage IIIC or stage IV melanoma in patients harboring a BRAF mutation. The inhibitor targets the common V600E BRAF mutation. Interim analysis of 675 patients revealed superiority in OS and PFS for vemurafenib. The response rate of patients on vemurafenib was 48.4% compared to 5.5% for patients receiving dacarbazine. While such a response rate for single modality therapy was essentially unprecedented in the treatment of metastatic melanoma, enthusiasm was tempered, at least to some extent, by the observation that disease recurrence has been observed in the majority of patients 6 to 8 months following initiation of therapy. Also important was the observation that up to 25% of patients who received vemurafenib developed squamous carcinoma of the skin, often in the form of keratoacanthomas. Dabrafenib (GlaxoSmithKline), another agent targeting BRAF V600 mutant melanoma, demonstrated similarly high OR rates in a phase III trial; together, these findings provided the basis for approval of each of these agents as monotherapy in 2011 and 2013, respectively.

MEK, a kinase downstream of RAF in the MAPK pathway, has been targeted in a similar fashion. MEK inhibitors also demonstrated benefit as monotherapy in patients with BRAF-mutant metastatic melanoma, leading to the FDA approval of trametinib in 2013. Of note, MEK inhibitors are rarely used as monotherapy for patients with BRAF-mutant metastatic melanoma.

Identification of mechanisms of resistance comprises an active component of contemporary melanoma research, a goal of which is to identify potential combinatorial approaches that may reduce resistance pathways and promote durable response. Numerous studies have elucidated acquired mechanisms of therapeutic resistance to BRAF-targeted therapy, and insights gained have led to treatment strategies to enhance responses to therapy. An outcome of this is the use of combined

BRAF and MEK inhibition—based on the observation that most BRAF-mutant melanomas demonstrate MAPK pathway reactivation at the time of therapeutic resistance. This combination was tested in clinical trials in patients with BRAF-mutant melanoma, and results suggested that treatment with combined BRAF and MEK inhibition (e.g., dabrafenib plus trametinib vs. dabrafenib monotherapy) was associated with a higher overall response (76% vs. 54%), and with a longer PFS (9.4 vs. 5.8 months) than with BRAF inhibitor monotherapy. In January 2014, the FDA granted accelerated approval to combined dabrafenib and trametinib for use in combination in patients with unresectable or metastatic BRAF-mutant melanoma. The following year, the FDA also approved the BRAF/MEK inhibitor combination of vemurafenib and cobimetinib. It should be noted that BRAF inhibitors have been shown to paradoxically stimulate growth in patients with wild-type BRAF status. Recently published data from the COMBI-MB clinical trial that enrolled patients with melanoma brain metastases to receive dabrafenib and trametinib; across four patient cohorts, intracranial response ranged from 44% to 59%, although duration of response was relatively short.

KIT Inhibitors

KIT mutations have been another therapeutic target for patients with metastatic melanoma. Several case reports had demonstrated a benefit for individual patients who were treated with a KIT inhibitor. Carvajal et al. published the results of a phase II study of 28 patients with unresectable metastatic melanoma who had KIT mutations and were treated with imatinib mesylate. In this study, 16% of patients had durable responses that lasted more than a year. Currently, a number of clinical trials are investigating the targeting of both KIT and NRAS mutations.

Immunotherapy

Immunotherapy can be broadly characterized as a therapy that enhances the host’s cellular immune response to cancer. To date, available options include agents that (1) increase the general, albeit nonspecific proliferation of the immune system (high dose Il-2), (2) the highly specific alleviation of inhibitory regulators of tumor surveillance (immune checkpoint blockade), (3) the in vitro expansion and subsequent transfer of autologous immune cells (adoptive cell therapy [ACT]), or (4) a combination of any of the above.

Interleukin-2

Interleukin-2 (IL-2) promotes the proliferation, differentiation, and recruitment of T, B, and NK cells and initiates cytolytic activity in a subset of lymphocytes. Although high-dose IL-2 has overall response rates of only 10% to 15% in appropriately selected patients, it is generally durable among the fraction of patients who have a complete response; such durability of response was associated with approval by the U.S. FDA for metastatic melanoma in 1998. However, IL-2 administration is associated with multiple side effects, including, but not limited to the uncommon but potentially life-threatening "capillary leak syndrome." Therefore, it should be administered only by clinicians and teams experienced in the management of such therapies.

Immune Checkpoint Blockade

Ipilimumab is a humanized monoclonal antibody that blocks CTLA-4, a key regulatory molecule of the immune system. In a phase III, randomized prospective trial, Hodi et al. evaluated 676 patients who received ipilimumab, ipilimumab plus a peptide vaccine, or peptide vaccine alone. Overall response and disease control were highest in the ipilimumab alone cohort. Median OS was 10.1 months for this cohort and overall response was 10.9%. Disease control was 28.5%, with 60% of the ipilimumab cohort having a significant response at 2 years.

In March 2011, the FDA approved ipilimumab as a second-line treatment for metastatic melanoma. A more recent study demonstrated the benefit of ipilimumab in the first-line setting. In a phase III, double-blind clinical trial of 502 metastatic melanoma patients randomized to ipilimumab plus dacarbazine versus placebo plus dacarbazine by Robert et al., the ipilimumab cohort was associated with a significantly higher OS (11.2 months vs. 9.2 months) and durable response (19.3 months vs. 8.3 months).

As mentioned in the adjuvant section above, ipilimumab dosing has been studied at multiple levels and schedules. For patients with metastatic melanoma, the currently approved ipilimumab dose is 3 mg/kg by intravenous infusion given every 3 weeks for four doses. A randomized phase II trial found that the objective response rate and OS increased progressively with increasing the dose to 10 mg/kg. However, serious immune-related adverse events, including drug discontinuations, also increased with dose escalation. Ipilimumab dosing was studied further in a

European phase III randomized trial of 727 patients who were randomized to 3 mg/kg or 10 mg/kg. Preliminary results were presented at the 2016 European Society for Medical Oncology (ESMO) meeting. Overall survival was significantly increased with the higher dose of ipilimumab (3-year OS 31.2% vs. 23.2%, median 15.7 vs. 11.5 months, HR 0.84, 95% CI 0.70 to 0.99). As expected, rates of grade 3 to 5 adverse events and immune-related adverse events were significantly higher with the 10 mg/kg schedule (34.3% vs. 18.5% and 33.5% vs. 17.4%, respectively).

The next major immune checkpoint axis studied was the programmed cell death protein-1 (PD-1) axis, which functions in the periphery to modulate T cell responses. PD-1 interacts with two ligands that are members of the B7-like molecules (PD-L1 & PD-L2) to dampen T cell responses, physiologically functioning to limit autoimmunity. The inhibitory effect of PD-1 is accomplished through a dual mechanism of promoting apoptosis in cytotoxic T-cells (programmed cell death, as the name implies) while simultaneously reducing apoptosis in regulatory T cells (Tregs). PD-1 protein is upregulated on activated T cells, with blockade of this molecule resulting in the cellular immune system's antitumor activity by inhibiting this naturally occurring negative feedback mechanism.

The clinical use of PD-1 blocking antibodies has been tested in several clinical trials, including a phase I trial of 296 patients with either advanced melanoma or other solid tumors. Treatment with a monoclonal antibody targeting PD-1 (nivolumab) was associated with a 28% response rate in patients with metastatic melanoma, with long-term responses longer than 1 year in 50% of responders. Anti–PD-1-based therapy was associated with a lower rate of grade 3 or 4 AEs compared to ipilimumab. Additional clinical trials have been performed (NCT01295827/NCT01704287), including a phase III trial with over 500 patients with metastatic melanoma whose disease was refractory to CTLA-4 blockade. In this trial (KEYNOTE-002), patients were randomized to pembrolizumab (2 mg/kg every 3 weeks), pembrolizumab (10 mg/kg every 3 weeks) or chemotherapy (carboplatin plus paclitaxel, paclitaxel alone, dacarbazine, or temozolomide per institutional standard). PFS was the primary endpoint and was significantly improved with both pembrolizumab arms compared to chemotherapy; 6-month PFS was 34%, 38%, and 16% for pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy, respectively.

Toxicity was limited in this trial; the most common adverse events included fatigue, pruritus, and rash. Grade 3 immune related adverse events (IRAE) were seen in two patients treated with pembrolizumab 2 mg/kg (hepatitis, hypophysitis), and in eight patients who received pembrolizumab 10 mg/kg (hepatitis, colitis, pneumonitis, and iritis or uveitis).

Cellular Therapies

Cellular or adoptive cell therapy (ACT) involves the in vitro expansion and activation, to superphysiologic numbers ($10^{10\text{-}12}$), of highly specific cytotoxic T-cells directed against a patient's own tumor and re-infusion after a lymphodepleting preparative regimen. These were originally procured by resection of a metastatic deposit and the growing of so-called TIL. More recently, these cytotoxic lymphocytes have been created by gene modification of a patient's peripheral blood mononuclear cells (PBMCs) or the creation of chimeric antigen receptors (CARs) that further advance specificity and are not dependent upon a resectable lesion. At the U.S. National Cancer Institute (NCI), Rosenberg and others have reported their experiences with ACT using TIL generally derived from metastatic tumors. An overall response rate as high as 72% was seen in patients with stage IV disease treated with ACT, with the addition of an extensive immune depletion preparative regimen (lymphodepleting chemotherapy + 12-Gy total-body irradiation [TBI]). A randomized, prospective study by the same group did not support the role of added TBI, but nonetheless report impressive overall response rates of 56%. Key steps affecting response include the effectiveness of lymphodepletion prior to T cell transfer, extranodal source of TIL, short culture duration, short TIL doubling time, greater autologous tumor lysis by TIL, and TIL secretion of granulocyte–macrophage stimulating factor. Cellular therapies are becoming much more specific with far less "off target" toxicity due to prior mentioned genetic modification. Recent evidence from the NCI suggests that neoantigens and their respective T cell receptors (TCR) can be identified in both tumors (including metastatic uveal) and in peripheral blood. Once procured, these can be massively expanded in vitro for subsequent infusion. Additional approaches employing in vitro pulsed dendritic cell infusion are also ongoing. Importantly, since these techniques require specialized expertise and an elaborate infrastructure, it is currently only available in select academic centers worldwide.

Combinatorial Strategies

Given the differential mechanisms of action of CTLA-4 blockade and PD-1 blockade, their use in combination has been explored; pre-clinical data and clinical trials demonstrated enhanced antitumor activity for the combination-based approach. However, the clinical benefit is associated with increased toxicity. In the largest phase III clinical trial combining anti–PD-1 and anti–CTLA-4 checkpoint inhibition (CheckMate 067), over 900 treatment-naive patients were randomly assigned to nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 3 weeks) for four doses followed by nivolumab (3 mg/kg every 2 weeks), nivolumab alone (3 mg/kg every 2 weeks), or ipilimumab alone (3 mg/kg every 3 weeks for four doses). The primary endpoints of this trial were PFS and OS. At a median follow-up of 12 months, the median PFS for the combination arm or the nivolumab arm alone were superior to ipilimumab alone (11.5 vs. 2.9 months and 6.9 vs. 2.9 months, respectively). Not surprisingly, serious toxicities were more frequent with the combination than with either monotherapy arm alone. Despite the toxicity and based on survival data, the FDA granted accelerated approval in 2015 for the combination of ipilimumab and nivolumab for stage IV disease. Given the toxicities associated with this combination checkpoint inhibitor regimen, additional combinations are being explored, including combinations with other novel checkpoint inhibitors and other modalities such as targeted therapy. As an example, in the Phase 1b KEYNOTE-029 clinical trial, standard dose pembrolizumab was used in combination with reduced-dose ipilimumab for patients with advanced melanoma, and overall was noted to be associated with a manageable toxicity profile and robust antitumor activity. Additional studies are underway to better define such regimens.

Tumor Vaccines

Tumor vaccines have also been explored for the treatment of advanced melanoma and as adjuvant therapy for patients with high-risk melanoma. These vaccines may contain (1) irradiated tumor cells, usually obtained from the patient (2) partially or completely purified melanoma antigens or (3) tumor cell membranes from melanoma cells infected with virus (viral oncolysates). Synthetic vaccines containing genes that encode for tumor antigens and peptide antigens themselves are also being evaluated, as are vaccines containing genes encoding for immune costimulatory signal proteins.

Allogeneic tumor cell vaccines, generally prepared from cultured cell lines or lysates thereof, offer several potential important advantages over autologous tumor cell vaccines. Allogeneic vaccines are readily available and can be standardized, preserved, and distributed in a manner akin to any other therapeutic agent. To date, the majority of studies involving allogeneic tumor vaccines have been small, single-institution studies. None of these have demonstrated an unequivocal benefit for immunotherapy with allogeneic tumor cells administered in conjunction with BCG compared to no treatment or to treatment with BCG alone.

Additional vaccine strategies include administration of synthetic peptides based on known melanoma T-cell antigens, genetic vaccines, and combinations of vaccines with cytokines or costimulatory molecules. Morton et al. conducted nonrandomized studies of a polyvalent melanoma vaccine (Canvaxin) in patients with stage III or stage IV disease. Although matched-pair analyses of data from phase 2 trials demonstrated a consistent OS benefit for Canvaxin therapy in stage III or stage IV melanoma, two separate randomized phase III clinical trials of Canvaxin in patients with stage III or IV melanoma, however, were discontinued due to lack of potential benefit based on interim analyses.

Chemotherapy

Single-agent chemotherapy has historically been a standard of care for systemic chemotherapy in patients with metastatic melanoma, but response rates remain quite poor. Dacarbazine has generally been a drug of choice, with a response rate of 16%. Other drugs, including cisplatin, paclitaxel, docetaxel, and the dacarbazine analog, temozolomide, have also shown activity in this disease. In general, even when metastatic melanoma responds to systemic chemotherapy, the duration of the response is usually short, in the range of 3 to 6 months (see also Biochemotherapy below).

Biochemotherapy

Multiple trials have investigated the potential benefit of combining biologic therapy with chemotherapy, an approach known as biochemotherapy. Overall, although biochemotherapy was associated with higher response rates and longer median survival than chemotherapy alone in several relatively small trials, a meta-analysis of chemotherapy versus biochemotherapy performed in 2007 concluded that there was no

advantage in either arm for duration of response or OS; biochemotherapy, however, was superior in delaying disease progression, and in rates of partial or complete response. Currently, biochemotherapy is infrequently employed for patients with metastatic melanoma.

Radiation Therapy

Wide excision is the standard treatment for primary melanoma, but radiation treatment has been occasionally performed in patients who have been deemed inoperable for various reasons (e.g., severe medical comorbidities). In one study of 95 invasive melanomas treated with high-dose radiation, the 5-year survival was 70%. In cases in which the local recurrence rate is high (e.g., inability to obtain adequate margins, desmoplastic melanoma), adjuvant radiation to the primary site is a consideration.

The role of adjuvant radiation to regional lymph node basins has also been explored. Several retrospective studies have demonstrated that lymph node basins with multiple tumor-involved nodes, one or more metastatic lymph nodes larger than 3 cm in diameter, extracapsular extension, or recurrent regional disease may benefit from adjuvant radiation, although toxicity from this approach has tempered enthusiasm, particularly for patients in whom radiation to the groin is being considered. Importantly, a randomized controlled trial from Australia examined 234 patients at high risk for regional recurrence after lymphadenectomy. These patients were stratified to either observation or 48 Gy of radiation. The observation group had a 26.8% recurrence rate versus 20% for the adjuvant radiation group. Overall survival, however, was not found to be different. The importance of local control in reducing morbidity, however, should not be underestimated, and future research goals may include randomized clinical trials to further define the role of adjuvant radiation therapy alone or in combination with systemic therapy. In general, patients with multiple involved or matted regional nodes or with extracapsular extension of regional lymphatic metastases may be considered for adjuvant radiation therapy in the context of the multidisciplinary care of the patient with metastatic melanoma.

External-beam radiation therapy can provide long-term local control and effective palliation in some patients with advanced melanoma. Symptomatic bone metastases from melanoma also frequently respond to external-beam radiation therapy. In addition, recurrent subcutaneous and

nodal disease can also sometimes be treated in this fashion, although significant advances in the treatment landscape of metastatic melanoma have reduced the overall use of these approaches.

FOLLOW-UP AND SURVEILLANCE

Melanoma has a more variable and unpredictable clinical course than almost any other human cancer. At MD Anderson, the schedule of follow-up evaluations for patients with melanoma varies according to the risk of recurrence. In general, patients with early-stage invasive melanoma (e.g., ≤1-mm tumor thickness, nonulcerated, lymph-node negative) have follow-up visits every 6 months for 2 years and then annually. Patients with thicker or ulcerated melanomas and those with positive lymph nodes generally return for follow-up visits more frequently—every 3 to 4 months up to 3 years, every 6 months during years 3 and 4, and annually thereafter. At each visit, the patient undergoes a physical examination concentrating on skin survey and lymph node basin exam. Abnormal findings may prompt further workup. Extensive radiographic evaluation of asymptomatic patients with AJCC stage I or stage II melanoma who are clinically free of disease rarely reveals metastases and thus is not routinely performed. Radiographic evaluation is generally performed for patients with microscopic stage III disease prior to adjuvant therapy, and selectively prior to completion lymphadenectomy for a positive SLN. CT or PET/CT should be considered every 3 to 12 months (or according to clinical trial, if participating) to evaluate for recurrent or new metastatic disease in patients with stage III or IV disease. MRI of the brain is also often performed for surveillance in patients who are stage IIIC or IV. The role of ultrasound for surveillance of regional lymph node basins is not well defined, although should be strongly considered for patients who have a positive SLN and do not undergo CLND.

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4 Nonmelanoma Skin Cancer

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EPIDEMIOLOGY AND ETIOLOGY

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) constitute the majority of nonmelanoma skin cancers (NMSCs) which are also referred to as “keratinocyte cancer.” Keratinocyte cancer represents about 95% of malignant skin tumors estimated at greater than 3.5 million cases annually. While BCC is four to five times more common than SCC, the incidence of both tumor types continues to rise despite growing awareness of the risk factors for these skin cancers. The overall incidence increases with age and is known to be higher in men than in women.

Development of NMSC is multifactorial and is related to various genotypic, phenotypic, and environmental risk factors. Ultraviolet (UV) solar radiation is considered to be the dominant risk factor for the development of both BCC and SCC, supported by the fact that most of these tumors tend to present on sun-exposed areas of the body. The development of BCC is thought to arise from intense intermittent sun exposure leading to burns, whereas SCC appears to be linked to the cumulative dose of UV solar radiation over time. Sun exposure earlier in life appears to be more influential in skin cancer development than that received later in life. Markers of UV sensitivity (e.g., fair skin, light eyes, blond or red hair) and intensity of exposure (i.e., increased incidence for individuals living in proximity to the equator) are associated with increased NMSC risk as is additional UV exposure from recreational tanning booths and UV light therapy. One case-controlled study demonstrated that the use of tanning devices was associated with an estimated twofold risk for both SCC (odds ratio = 2.5) and BCC (odds ratio = 1.5). Karagas et al. reported that treatment of psoriasis with oral psoralen in combination with light treatment (PUVA therapy) resulted in an increased adjusted relative risk of 8.6 for SCC while the risk for BCC was much lower. UV-induced mutations in the p53 tumor suppressor gene

is thought to be a common event in NMSC development.

Another important risk factor for both BCC and SCC is immunosuppression. Long-term immunosuppression therapy such as that used for solid organ transplant has been shown to increase the risk of SCC over 100-fold and for BCC about 10-fold. SCC in immunosuppressed patients tend to be behave more aggressively and are associated with greater tumor depth, higher risk of recurrence, and more frequently associated with perineural or lymphovascular invasion. However, BCCs have not been found to be more aggressive in solid organ transplant recipients than the general population. Patients with acquired immunodeficiency syndrome also have an increased incidence of NMSC, and factors such as persistent human papilloma virus (HPV) infection may act synergistically with UV exposure to increase risk. Moreover, HPV infection, especially HPV 16 and 18, has been implicated in the development of anogenital SCC.

Exposure to ionizing radiation increases the risk of NMSC threefold and often presents decades after initial exposure. This risk has been shown to be dose dependent. Chemical exposures such as arsenic, tar, soot, tobacco, asphalt, and mineral oil have all been associated with an increased risk of SCC. SCC can also arise from areas of chronic inflammation and healing such as from scars, burn sites, or ulcers; this type of SCC is also known as a Marjolin ulcer.

Patients with genetic syndromes including xeroderma pigmentosum, albinism, Muir–Torre syndrome, dystrophic epidermolysis bullosa, Fanconi anemia, Werner syndrome, nevoid basal cell syndrome, and Li–Fraumeni syndrome have an increased incidence of NMSC. Xeroderma pigmentosum is a rare autosomal recessive disease characterized by photophobia, severe sun sensitivity, and advanced sun damage. Affected individuals have defective DNA excision repair, and when exposed to UV radiation, develop malignancies of the skin and eyes at a rate 1,000 times that of the general population. Aggressive sun protection in the form of full-body sun suits and regular skin examinations are critical for patients with xeroderma pigmentosum. Ideally, these patients should only go outside at night. Nevoid basal cell syndrome is an autosomal dominant disorder characterized by the development of multiple BCCs. BCCs in patients with nevoid basal cell syndrome are often quite small but can number in the hundreds on any given skin surface. The sonic hedgehog signaling pathway (PTCH1 gene, chromosome 9q) has been recognized as

having a significant etiologic role in nevoid BCC syndrome, and is also present in 90% of sporadic BCC. These patients are exquisitely sensitive to radiation and should avoid excessive sun exposure and radiation therapy. Regular follow-up is important, as such tumors are difficult to monitor and treat.

Similar to other tumor types, a previous diagnosis of cutaneous carcinoma increases the risk of future NMSCs to as high as 35% at 3 years and 50% at 5 years.

DIFFERENTIAL DIAGNOSIS

Several epidermal tumors common to the skin can resemble or are precursors to NMSC. Recognition of these tumors is important for both tumor surveillance and cancer prevention.

Seborrheic keratoses are benign proliferations of epidermis that can appear on any part of the skin, except mucous membranes, and usually appear after the age of 30 years. They are not related to sun exposure but are common on the face, neck, and trunk, often in large numbers. They initially appear as flat brown macules, eventually becoming larger, “stuck-on” brown plaques with dull crumbly surfaces (Fig. 4.1A). Seborrheic keratoses can sometimes be confused with melanoma, and biopsy of these lesions is prudent if any sudden changes in size or color occur.

B

C

Figure 4.1 **A:** Seborrheic keratosis. (Reprinted with permission from Elder DE. *Lever's Histopathology of the Skin, 11th ed*. Philadelphia, PA: Wolters Kluwer; 2014.) **B:** Actinic keratosis. (Reprinted with permission from Rose M. *Oncology in Primary Care*. Philadelphia, PA: Wolters Kluwer; 2013.) **C:** Cutaneous horn. (Reprinted with permission from Elder DE. *Lever's Histopathology of the Skin, 11th ed*. Philadelphia, PA: Wolters Kluwer; 2014.)

Actinic keratoses (AKs) are premalignant lesions with the potential to develop into SCCs. They are found mainly on sun-exposed areas. These lesions most commonly present as skin-colored, erythematous, or brown ill-defined patches with adherent scales (Fig. 4.1B). These lesions are extremely common on the face, scalp, ears, and lips and can often be better appreciated by palpation rather than by inspection with the naked eye.

Keratoacanthoma is a tumor that often occurs on older, sun-damaged skin and is most commonly found on the neck and face. These tumors originate in pilosebaceous glands and may grow rapidly as a red- or skin-colored dome-shaped nodule with a central crater. Maximum size may be attained at 6 to 8 weeks with slow regression over a period of months leaving a residual scar. These tumors can be confused both clinically and histologically with SCC, and there are reports of progression of keratoacanthomas to invasive or metastatic carcinoma. Classification of these tumors as a well-differentiated variant of invasive SCC has been proposed. Surgical excision of keratoacanthomas with 3- to 5-mm margins is recommended, and Mohs surgery may be employed in cosmetically sensitive areas. These tumors are radiation sensitive if surgery is not an option.

A cutaneous horn is the clinical description for a growth that appears as a dense cone of epithelium resembling a horn (Fig. 4.1C). They range in size from several millimeters to over a centimeter and are generally white or yellowish in color; they also tend to appear on sun-exposed skin of older individuals. Histologically, cutaneous horns can develop from benign lesions such as warts or seborrheic keratoses, from premalignant lesions such as AKs and SCCs in situ or from malignant lesions such as SCCs. Up to 15% of cutaneous horns demonstrate invasive SCCs at the base, and excision of these tumors is always indicated.

Nevus sebaceous is a benign tumor of the scalp that appears at or soon after birth as a yellowish-orange, well-demarcated plaque. Initially, the

surface has a smooth or waxy appearance that gradually becomes more warty or verrucous during puberty. In adulthood, approximately 10% of these lesions develop into BCC. It is therefore recommended that these lesions be excised or closely monitored for the life of the patient.

BASAL CELL CARCINOMA

BCC is the most common cancer in humans and the most common type of skin cancer. BCCs are believed to arise from hair follicle cells and are therefore found almost exclusively on hair-bearing skin. Most lesions are found on sun-exposed mask areas of the head and neck, but non–sun-exposed areas are also at risk. These tumors tend to grow slowly, but when untreated can lead to invasion of local structures including muscle, cartilage, and bone. Although the biologic behavior of BCC is characterized by local and sometimes disfiguring invasiveness, metastasis is rare, occurring in less than 0.05% of cases.

There are multiple histologic subtypes of BCC, and subtype is predictive of its behavior. Less aggressive subtypes include nodular or superficial BCC, along with keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus. Higher-risk subtypes include sclerosing, infiltrating, micronodular, morpheaform (or desmoplastic), and basosquamous carcinoma. The higher-risk subtypes tend to have subclinical extension exceeding the visible borders of the lesion making treatment more difficult.

Nodular BCC is the classic lesion of this type of NMSC. It appears as a pink translucent nodule with rolled edges and is often described as “pearly.” In dark-skinned individuals, these tumors are often pigmented and can resemble melanoma. Overlying telangiectasias and ulceration are common (Fig. 4.2). They occur predominantly on the face.

Superficial BCC is a variant that is more common on the limbs and trunk, and on other areas with little or no sun exposure. It presents as a slow-growing, scaly pink plaque and can easily be confused with psoriasis, superficial SCC or SCC in situ (Bowen disease). Gentle traction on the periphery of the lesion often demonstrates a shiny translucent surface characteristic of BCC which can assist with diagnosis.

Figure 4.2 Nodular basal cell carcinoma. (Reprinted with permission from Elder DE. *Lever's Histopathology of the Skin, 11th ed*. Philadelphia, PA: Wolters Kluwer; 2014.)

The sclerosing or morpheaform type represents the rarest form of BCC and is often difficult to recognize. It presents as a poorly defined indurated or sclerotic plaque which can be mistaken for a scar. In addition, this type of BCC frequently is found to be larger histopathologically than is clinically evident. Therefore, both diagnosis and treatment remain a challenge.

Basosquamous carcinomas have histologic features of both BCC and SCC. Some of these lesions occur as a result of collision between adjacent BCC and SCC. These are aggressive tumors with potential to metastasize, though metastatic risk is determined by the degree of squamous component present.

SQUAMOUS CELL CARCINOMA

SCC is the second most common cutaneous carcinoma and accounts for roughly 20% of all NMSCs. In addition, SCC is responsible for the majority of deaths from NMSC. SCC develops from keratinocytes of the epidermis and has many clinical variants. As stated previously, it can arise from precursor lesions such as AK or can develop at the base of a

cutaneous horn. Uncommonly, SCC presents de novo as a single lesion on otherwise normal appearing skin. The most common lesion is found on sun-damaged skin, especially on the head, neck, or arms. The lesions are usually red, poorly defined plaques or nodules with an ulcerated friable surface (Fig. 4.3). Bowen disease, or SCC in situ, is characterized by a rapidly growing, well-demarcated ulcerating tumor in a pre-existing scaly, erythematous plaque. Up to 5% of Bowen disease may become invasive.

SCC has a higher metastatic potential than BCC, with an overall 5-year recurrence and metastatic risk of 8% and 5%, respectively. However, many factors affect the metastatic potential of any given tumor, and there are subgroups with higher risk (Table 4.1). Regional lymph nodes are the most common metastatic site, with distant sites such as bone, brain, and lungs occasionally reported. For tumors of the head and neck, the parotid gland is a common site for metastases. In general, features that indicate high risk for metastasis also predict risk for recurrence.

Figure 4.3 Squamous cell carcinoma. (From Goodheart HP, MD. *Goodheart's Photoguide of Common Skin Disorders, 2nd Edition*. Philadelphia: Lippincott Williams & Wilkins, 2003, with permission.)

WORK-UP/BIOPSY TECHNIQUES

Work-up of any NMSC should include a thorough history, including reported duration, rate of growth, associated symptoms, previous treatment, and risk factors for NMSC. Changes noted by the patient may be quite subtle and include itching, tenderness, bleeding, or changes in size, color, or texture. A detailed head-to-toe skin examination should be performed with careful inspection and palpation of suspicious lesions. In patients suspected of having SCC, the draining lymph node basins should be evaluated for nodal metastases by palpation. In general, radiologic studies are not necessary for the evaluation of patients with SCC, however, if high-risk features are present a magnetic resonance imaging study can be obtained to evaluate the extent of tumor involvement and ultrasound can be used for the evaluation of regional nodal basin(s).

Any cutaneous lesion suspicious for malignancy should be biopsied for pathologic assessment. Biopsy of suspicious pigmented lesions should be limited to punch or excisional biopsy techniques in which the full thickness of the dermis can be evaluated. A punch biopsy usually ranges in size from 2 to 8 mm and involves removing a cylinder of tissue, ideally to the level of the subcutaneous fat. Often, entire lesions can be removed for pathologic examination; if not, the most suspicious aspect of the tumor may be sampled.

Shave biopsy is an excellent technique for superficial lesions or nonpigmented lesions suspicious for BCC or SCC. It is also a good biopsy technique for cutaneous horns or keratoacanthomas provided the base of the tumor is included in the specimen. A shave biopsy involves injecting local anesthesia into the epidermis and upper dermis and then performing a tangential sample at the base of the wheal. A sterile flexible razor blade or a 15 blade is recommended so that the mid-dermis is included in the biopsy specimen. If performed too superficially, invasion into the dermis cannot be evaluated and rebiopsy may be required.

Excisional biopsy involves removal of the entire lesion with a margin of clinically clear tissue and is generally used for classic lesions such as superficial SCCs or nodular and superficial BCCs. Margins can be evaluated in the specimen, and further treatment is often unnecessary.

TABLE 4.1 Risk Factors for Recurrence and Metastases in Squamous Cell Carcinoma

	Low-Risk Feature	High-Risk Feature
Clinical Factors		
Tumor size	<2 cm	>2 cm
Location	Trunk, extremities	Mucosal surfaces, genitalia, mask areas of face including eyelids, periorbital, nose, lips, chin, pre- and postauricular areas, ear, and prior burn scars or irradiated areas
Borders	Well defined	Ill defined
Arising from scar, inflammation	No	Yes
Prior radiation	No	Yes
History of immunosuppression	No	Yes
Primary vs. recurrent	Primary	Recurrent
Histology		
Differentiation	Well differentiated	Poorly differentiated
Perineural invasion	No	Yes
Lymphovascular invasion	No	Yes
Depth of invasion	<2 mm or < Clark level IV	≥2 mm or Clark level IV/V
Subtype	—	Bowen disease, desmoplastic SCC, acantholytic SCC, adenosquamous SCC, basosquamous SCC
Excision	Complete	Incomplete

A number of noninvasive diagnostic tools including dermoscopy, high-frequency ultrasound, optical coherence tomography, and confocal microscopy, have been investigated for screening, diagnosis, and management of NMSC. The benefits of these modalities are that they allow the examination of large affected areas and monitoring and surveillance of selected skin sites for topical treatment modalities (e.g., patients with AK or BCC treated with imiquimod).

STAGING

The 8th edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* states that there is no AJCC staging system for cutaneous SCC and BCC of the skin outside the head and neck. The details

of the head/neck staging are discussed further in Chapter 6.

TREATMENT

The treatment of NMSC requires careful evaluation of tumor size, pathologic characteristics, anatomical location, age, overall health of the patient, cost to the patient, and cosmesis. Treatment modalities can be divided into surgical and nonsurgical therapies although surgical intervention is often the mainstay of treatment.

Surgical Techniques

Primary surgical excision with a margin of clinically normal tissue allows subsequent evaluation of the entire specimen for clear margins. Complete excision with a margin of clinically normal tissue is associated with 5-year disease-free rates of over 98% for BCC and 92% for SCC. Predetermined margins of 4 to 10 mm should be performed along Langer lines to achieve the best cosmetic result (Fig. 4.4).

For well-defined, low-risk lesions <2 cm, excision with a 4-mm margin around the tumor border is expected to definitively treat the tumor in 95% of cases. For high-risk tumors, a larger margin of at least 6 mm is indicated, and European guidelines suggest at least 10-mm margin should be used. Recurrent BCC is associated with a poor cure rate and a 10-mm excision margin is recommended. For incompletely excised lesions, reexcision is recommended if possible.

Mohs micrographic surgery involves removal of the clinical margins of the tumor under local anesthesia with immediate evaluation of the margins with frozen sections. Small incremental sections are removed until the margins are clear. This technique allows for the best cosmetic results by preserving normal tissue, while ensuring that larger lesions with subclinical extension are entirely removed. Mohs micrographic surgery of primary and recurrent NMSC of the head and neck has a cure rate (negative histologic margin) of 97%. The reconstructive choices after Mohs surgery are similar to those available after traditional excision. Although Mohs micrographic surgery is time consuming and requires skilled practitioners, the benefits of superior cosmesis and excellent cure rates make it the treatment of choice for many patients. Indications for Mohs procedure are centrofacially located tumors, large tumors, poorly defined tumor margins, recurrent lesions, lesions with perineural or

perivascular involvement, tumors at a site of prior radiation therapy, tumors in the setting of immunosuppression, and patients with high-risk histologic subtypes of BCC.

There has been considerable interest in performing sentinel lymph node (SLN) biopsy in selected patients with high-risk SCC in hopes that detection and treatment of subclinical nodal metastases will lead to improved outcomes for these patients. In a pooled evaluation of 83 high-risk SCC patients, all patients with a positive SLN had lesions >2 cm in diameter. Among patients with tumors <2 cm, 2.1 to 3 cm, and >3 cm in diameter, the proportions of patients with a positive SLN were 0%, 15.8%, and 30.4%, respectively. While the available data suggest SLN biopsy can accurately identify micrometastatic nodal disease in patients with SCC, studies to date are limited by small sample size, limited follow-up, and lack of uniform criteria. Additional studies will be needed before definitive guidelines can be established with respect to SLN biopsy.

Destructive Techniques

Destructive techniques for superficial BCC and SCC include curettage, cryotherapy, and laser ablation. Curettage involves debulking the tumor under local anesthesia with a sharp curette until firm underlying dermis is reached. The base is hyfrecated, and the process is repeated two or three times. This technique is reserved for small (<1 cm), primary, low risk, or superficial tumors in non–hair-bearing areas, and as such is not suitable for recurrent or ill-defined tumors. The technique is based on the ability of the sharp curette to differentiate friable tumor tissue from normal dermis. If subcutaneous fat is reached during this technique, it is necessary to convert to surgical excision, as the curette will no longer be able to distinguish soft fat tissue from tumor.

Cryotherapy is a destructive method primarily reserved for the treatment of precancerous lesions such as AKs and occasionally for small, superficial, low-risk, primary BCCs or SCCs. Liquid nitrogen is either sprayed with a cryogen or is directly applied to the lesion with cotton-tipped applicators for a period of time such that the visible thawing of the lesions takes at least 15 seconds (30 seconds for superficial SCC or BCC). Ablation with a carbon dioxide laser may be considered for precancerous lesions or low-risk BCC. However, follicular involvement may be difficult to treat and lead to recurrence.

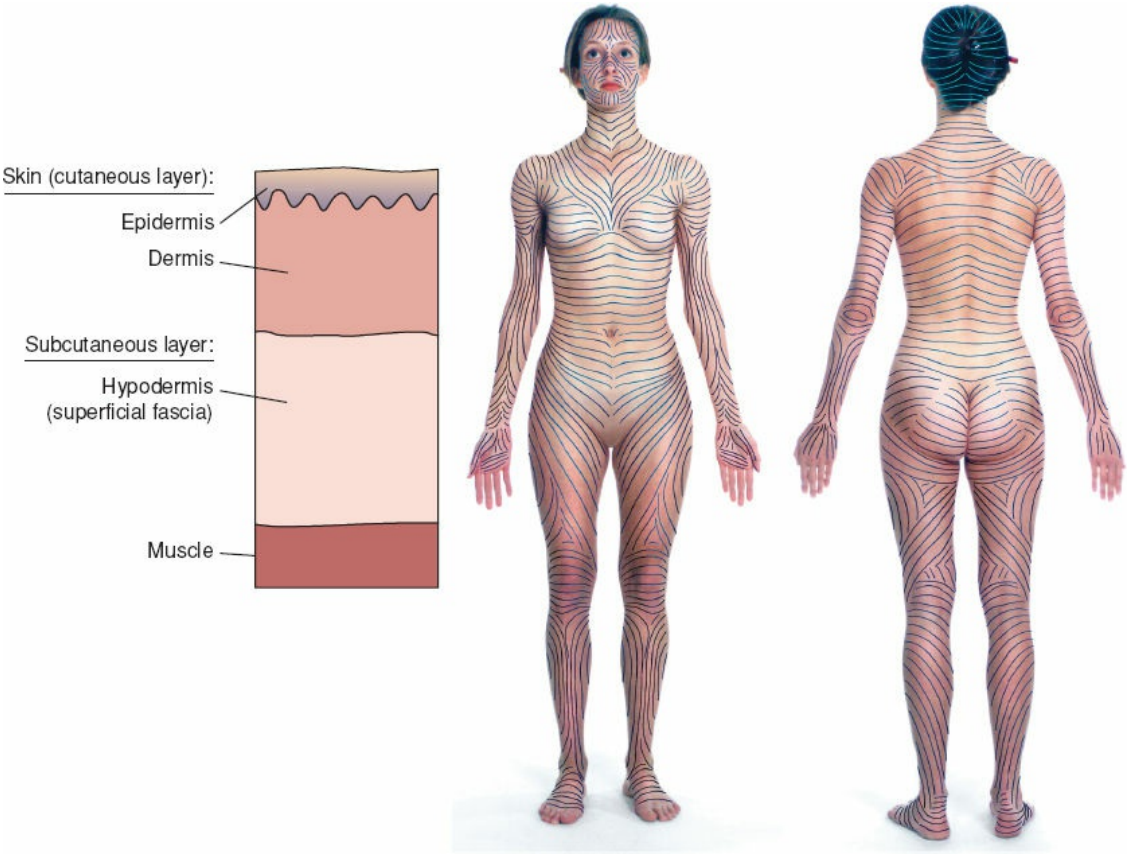

Figure 4.4 Langer lines. (Reprinted with permission from Clay JH, Allen L, Pounds DM. *Clay & Pounds' Basic Clinical Massage Therapy, 3rd ed*. Philadelphia, PA: Wolters Kluwer, 2015.)

Nonsurgical Therapies

Radiation therapy is often reserved for patients unable or unwilling to undergo surgical treatment of primary lesions or when clear margins cannot be obtained by Mohs or more extensive surgery. It is also widely accepted as adjuvant treatment of recurrent or histologically aggressive tumors particularly those with perineural invasion. For high-grade NMSC with perineural involvement or invasion into bone, radiation therapy is generally recommended in conjunction with surgical excision. Radiation therapy can be further used as adjuvant or palliative treatment for lymph node metastases. Disadvantages of radiation therapy include acute and chronic radiation changes (dyspigmentation, telangiectasia, radiodystrophy), higher recurrence rates in BCC, lack of margin control, and increased number of treatment sessions. As radiation therapy can result in NMSC decades after exposure, it should be used cautiously in young patients. It is also contraindicated in nevoid BCC.

Topical therapies for superficial NMSC and AKs include 5%

fluorouracil (5-FU) and imiquimod creams. 5-FU is an antineoplastic antimetabolite. Imiquimod is a synthetic immune response modifier that enhances cell-mediated immune response via the induction of proinflammatory cytokines. These topical therapies are most commonly used for AKs as well as for superficial BCCs and SCCs in situ when surgery or other treatment techniques are contraindicated or impractical. Topical 5-FU is not appropriate for nodular BCC and is not recommended for SCC due to high recurrence rates. Treatment regimens for AKs with 5-FU vary widely; in general, 5-FU is applied to the affected area once or twice daily for a period ranging from 2 to 6 weeks. Retreatment several months later, either with cryotherapy or other modalities, may be necessary. For the treatment of superficial BCC, 5-FU can be applied daily to the tumor and several millimeters of surrounding skin for a period of at least 4 weeks. After a 2- to 3-week respite, the area is then evaluated clinically for residual tumor. Biopsy is often indicated to ensure adequate therapy. Significant erythema, stinging, oozing, and crusting are often reported, especially with more aggressive treatment regimens. 5-FU can be applied to an entire region, such as the face, chest, arms, or hands.

Imiquimod therapy is approved for the treatment of AKs and superficial BCC but should not be used for SCC. In general, less local skin reaction is reported compared to 5-FU. For AKs the cream is applied 2 nonconsecutive days a week for 16 weeks. For superficial BCC, the cream should be applied 5 nights a week for at least 6 weeks. After a 2- to 3-month respite, the lesion is evaluated either clinically or histologically (rebiopsy) to confirm adequate therapy. While imiquimod can also be used for nodular BCC the treatment duration requires 12 weeks and the response is lower (76%) compared to a greater than 85% success rate for superficial BCC. Imiquimod is often well tolerated, causes minimal or no scarring, and is particularly useful for multiple lesions concentrated in one area.

Photodynamic therapy (PDT) is another noninvasive method used for the treatment of AKs and superficial BCC. A photosensitizer (most commonly, aminolevulinic acid) is applied to the skin and activated with a light source. The tumor cells retain the photosensitizer for longer periods of time than normal cells, resulting in preferential killing. Cure rates for AKs are reported to be as high as 90%; however, recurrence rates at 5 years for superficial and nodular BCC have been reported to be as high as 14% to 22%, respectively. Side effects include burning or stinging pain

during the treatment and posttreatment periods, erythema, swelling, and temporary hyper- or hypopigmentation, but overall the cosmetic results are superior in comparison to surgery or cryotherapy. Systemic PDT has also been tested as a treatment for BCC and may be appropriate for individuals presenting with multiple lesions or nevoid BCC syndrome.

Chemoprevention with low-dose oral retinoids has shown some promise in the prevention of SCC for chronically immunosuppressed patients who have undergone organ transplantation. However, long-term therapy is needed as beneficial effects are often lost when these drugs are discontinued.

SCREENING, PREVENTION, AND FOLLOW-UP

Aggressive screening of patients at risk for skin cancer is essential to minimize the morbidity and mortality of NMSC. Patients at risk include those with light skin types, immunosuppression, and a family or personal history of skin cancer. Exposure to UV radiation should be limited in children with regular use of broad-spectrum sunscreen from an early age. Appropriate SPF level and application techniques should be emphasized for all patients, especially regarding applications to the face and neck.

Regular examination of the skin by a dermatologist is recommended for all patients at risk for skin cancer on at least a yearly basis. A complete skin examination includes examination of the entire skin surface, including the scalp, with particular attention to previous areas of skin cancer. For patients with a history of AKs or NMSCs, regular follow-up with a dermatologist is recommended. For patients with SCC, most recurrences or metastases will occur within 2 years, and almost all will occur within 5 years. In addition, patients with a history of SCC should undergo a thorough examination of all regional lymph node basins to evaluate for metastases.

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5 Soft-Tissue and Bone Sarcoma

Naruhiko Ikoma, Christina L. Roland, and Barry W. Feig

SOFT-TISSUE SARCOMAS

Sarcomas are rare tumors; in 2016, the estimated number of new cases in the United States were 12,310 (0.7% of all new cancer cases), and the estimated number of deaths were 4,990 (0.8% of all cancer deaths), based on data from the Surveillance, Epidemiology, and End Results (SEER) database. At the time of presentation, 60% to 80% of patients have localized or regional (lymph node metastasis) disease, whereas 15% to 20% have metastatic disease. The overall 5-year survival rate for patients with all stages of soft-tissue sarcoma is 50% to 60% but varies significantly by stage (approximately 80% in patients with localized disease and 20% in those with metastatic disease). Of the patients who die of sarcoma, most will succumb to metastatic disease, which 80% of the time occurs within 2 to 3 years of the initial diagnosis.

Soft-tissue sarcomas arise predominantly from embryonic mesoderm but can also arise from the ectoderm. Mesodermal cells give rise to the connective tissues distributed throughout the body; therefore, soft-tissue sarcomas can occur anywhere in the body. The majority of primary lesions originate in an extremity (45%), with the next most frequent anatomic site of origin being intra-abdominal/retroperitoneal (40%), followed by trunk (10%) and head/neck region (5%) (Fig. 5.1). Sarcoma is a heterogeneous disease group that encompasses >60 histologic subtypes. Each subtype has its own unique behavior, different recurrence pattern, and distinct survival. Excluding gastrointestinal stromal tumors (GISTs), the most common histologic types of soft-tissue sarcoma in adults are undifferentiated/unclassified sarcoma (with pleomorphic, round cell, and spindle cell variants), leiomyosarcoma, liposarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor (MPNST) (Fig. 5.2). Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood.

For the past three decades, a multimodality treatment approach has been

applied to patients with soft-tissue sarcomas, which has improved treatment outcomes and quality of life. However, a significant number of patients with soft-tissue sarcoma will relapse and die, highlighting the need for improved systemic therapy options.

Etiology

The vast majority of sarcomas are sporadic with unknown etiology, but a number of factors have been associated with increased risk of soft-tissue sarcoma, including previous radiation exposure, chronic lymphedema, genetic predisposition, trauma, and occupational chemicals such as phenoxyacetic acids and wood preservatives containing chlorophenols.

Previous Radiation Exposure

External-beam radiation therapy is a rare but well-established cause of soft-tissue sarcoma. An 8- to 50-fold increase in the incidence of sarcomas has been noted for patients treated with radiation therapy for cancers of the breast, cervix, ovary, testes, and lymphatic system. In addition, the risk of developing a sarcoma after radiation therapy increases with higher dosage. The median latency between irradiation and the development of a sarcoma is approximately 10 years, but can range from 1 to 40 years. The most common histologic types of radiation-associated sarcomas are osteogenic sarcoma, undifferentiated/unclassified sarcoma, angiosarcoma, and lymphangiosarcoma. Radiation-associated sarcomas are associated with a worse prognosis compared with non–radiation-associated sarcomas, even when matched for stage.

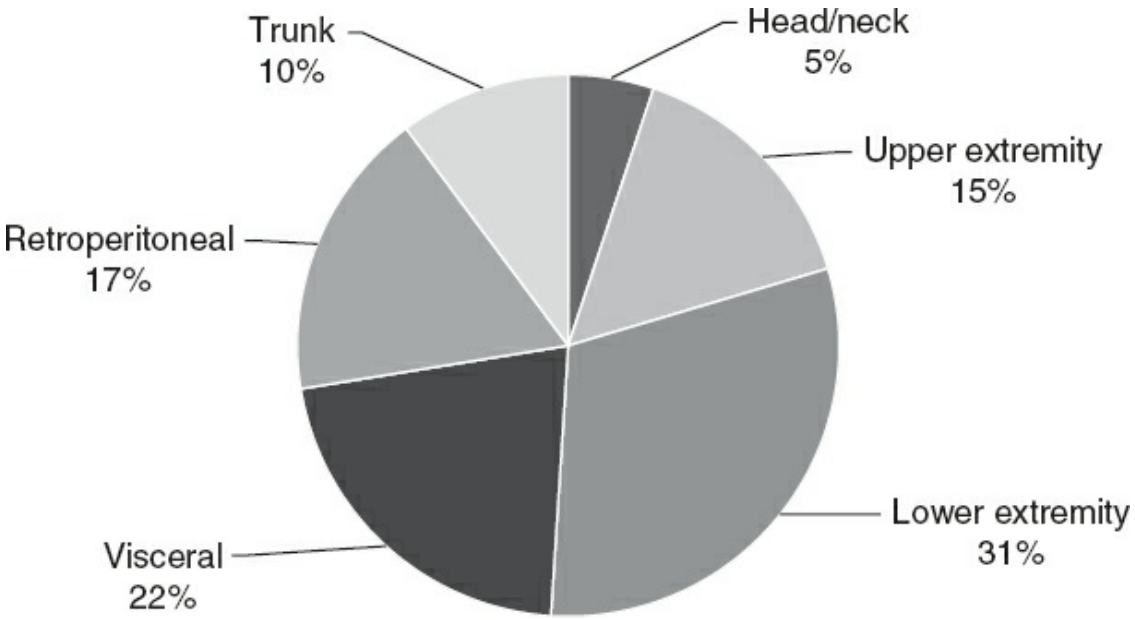


Figure 5.1 Distribution by location for adult patients with soft-tissue sarcoma. (Data from DeVita VT Jr., Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2015:1253–1291.)

Chronic Lymphedema

In 1948, Stewart and Treves were the first to describe the association between chronic lymphedema following axillary dissection and subsequent lymphangiosarcoma. Lymphangiosarcoma has also been observed in patients after filarial infections and in the lower extremities of patients with congenital primary lymphedema.

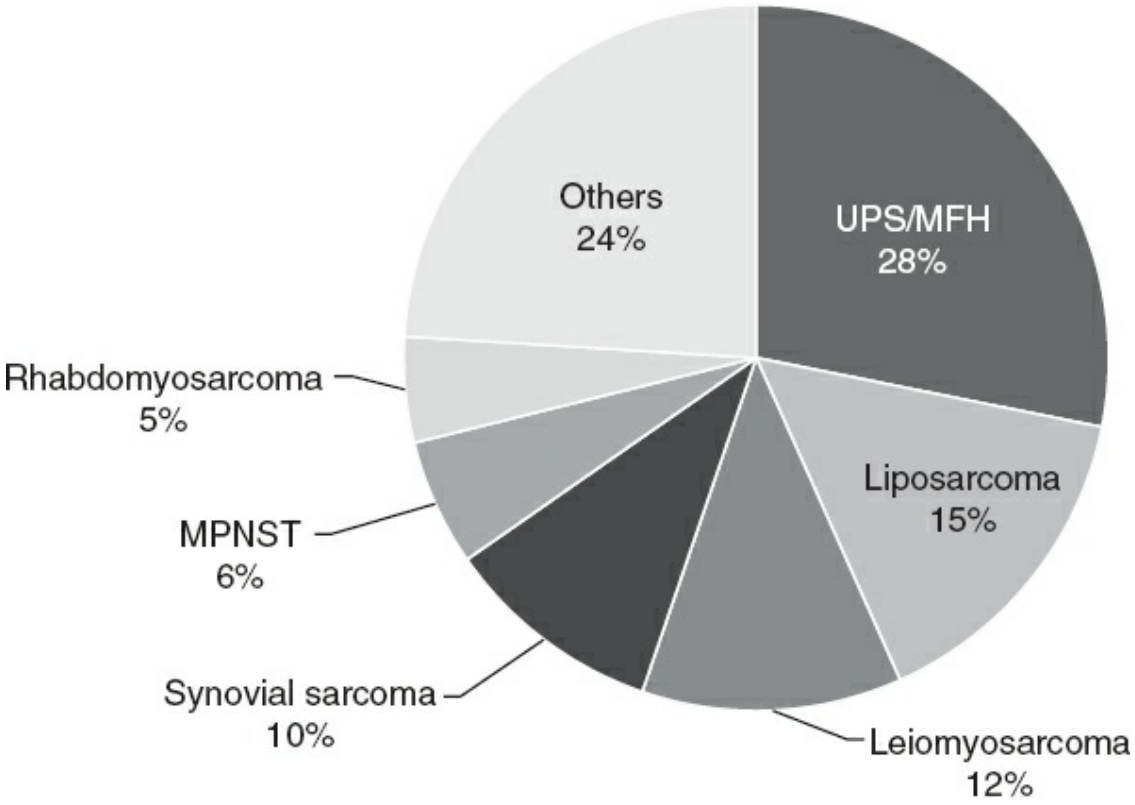


Figure 5.2 Common histologies of soft-tissue sarcoma. (Data from Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer* 2001;91:1914–1926.)

Genetic Predisposition

Several well-described genetic predisposition syndromes have been associated with increased risk of certain subtypes of bone and soft-tissue sarcomas. For example, patients with Gardner syndrome (familial adenomatous polyposis) have a higher than normal incidence of desmoid tumors; patients with germline mutations in the tumor suppressor gene *p53* (Li-Fraumeni syndrome) have a high incidence of sarcomas; and patients with von Recklinghausen disease who have abnormalities in the neurofibromatosis type 1 gene have an increased risk of MPNST. Soft-tissue sarcomas can also occur in patients with hereditary retinoblastoma as a second primary malignancy.

Several oncogenes have been associated with the development of soft-tissue sarcomas, including *MDM2*, *CDK4*, *N-myc*, *c-erbB2*, and members of the *ras* family. Amplifications of these oncogenes have been shown to correlate with an adverse outcome. Amplifications of MDM2 and CDK4

are frequently identified in well-differentiated or dedifferentiated liposarcomas and may be helpful in confirming histologic diagnoses as well as serving as potential treatment targets.

A number of chromosomal translocations have been associated with specific histologic subtypes. Several variants of translocations between chromosomes 11 and 22 have been reported in Ewing sarcoma; similarly, a fusion of two novel genes (SYT at 18q11 and SSX at Xp11), has been identified as a causative translocation in most (perhaps all) synovial sarcomas. Other translocations or gene rearrangements are best characterized in myxoid liposarcoma (FUS-DDIT3), alveolar rhabdomyosarcoma (PAX3-FOXO1), and desmoplastic small round cell tumors (EWS-WT1). Tumor suppressor genes, such as the retinoblastoma (*Rb*) and the *p53* gene, also play a critical role in many cases of soft-tissue sarcomas.

Histopathology

Despite there being numerous, heterogeneous subtypes, sarcomas share many clinical and pathologic features; therefore, traditionally, treatment regimens have been similar across the range of different subtypes. Histologic grade remains the most important prognostic factor for determining outcome. However, emerging data suggest that pathologic classification may better determine outcomes when other pretreatment variables are taken into account. Tumor behavior varies significantly among histologic subtypes; for example, lymph node metastasis is rare in soft-tissue sarcomas (<5%), except in a few histologic subtypes, such as epithelioid sarcoma, rhabdomyosarcoma, clear-cell sarcoma, angiosarcoma, and undifferentiated pleomorphic sarcoma (UPS). Metastatic potential also differs significantly among histologic subtypes. Table 5.1 shows a breakdown of the histologic types of tumors according to their metastatic potential.

Important updates were made in 2013 in the fourth edition of the World Health Organization's *WHO Classification of Tumours of Soft Tissue and Bone* (of note, there was an 11-year interval from the third edition). The updated edition incorporated many changes in tumor classification and provided new genetic insight into the pathogenesis of many different tumor types. In the update, a new category of undifferentiated/unclassified sarcomas was created, which includes undifferentiated pleomorphic, spindle cell, epithelioid, and round cell variants, and accounts for

approximately 20% of all sarcomas. The tumor previously known as malignant fibrous histiocytoma (MFH) falls into this category. Myxoid MFH was recategorized as a myxofibrosarcoma. The mixed-type liposarcoma category was deleted because these tumors likely represent dedifferentiated liposarcoma. The round cell liposarcoma category in the subset of high-grade myxoid liposarcoma was deleted since high-grade myxoid liposarcoma carries the same prognosis regardless of round cell or spindle cell morphology. *MDM2* or *CDK4* amplification is frequently found in well-differentiated and dedifferentiated liposarcomas; their role in distinguishing among these liposarcomas subtypes, however, has not been clearly defined. GIST, previously part of the digestive system classification, was included in the soft-tissue classification for the first time. Of note, historically, the term *atypical liposarcoma* was generally used to describe low-grade adipocytic tumors located in the extremity, whereas *well-differentiated liposarcoma* was generally used to describe pathologically similar adipocytic tumors which were located in the retroperitoneum, despite the fact that these two tumor types are pathologically identical. Currently, these terms are interchangeable.

TABLE **5.1** Breakdown of Sarcoma Histologic Type by Metastatic Potential

Low Metastatic Potential
Desmoid tumor
Atypical lipomatous tumor/Well-differentiated liposarcoma
Dermatofibrosarcoma protuberans
Hemangiopericytoma

Intermediate Metastatic Potential
Myxoid liposarcoma
Myxofibrosarcoma (previous myxoid malignant fibrous histiocytoma)
Extraskeletal chondrosarcoma

High Metastatic Potential
Undifferentiated pleomorphic sarcoma (previously pleomorphic malignant fibrous histiocytoma)
Liposarcoma (dedifferentiated and pleomorphic)
Leiomyosarcoma
Angiosarcoma
Alveolar soft-part sarcoma
Clear-cell sarcoma
Epithelioid sarcoma
Extraskeletal Ewing sarcoma
Extraskeletal osteosarcoma
Neurogenic sarcoma (malignant schwannoma)
Rhabdomyosarcoma
Synovial sarcoma

In as many as 25% to 40% of cases, expert sarcoma pathologists may disagree about specific histologic diagnoses or criteria for defining tumor grade. This low concordance rate may stem from the fact that few pathologists have the opportunity to study many of these rare tumors during their careers. It also emphasizes the need for more objective molecular and biochemical markers to improve the accuracy of conventional histologic assessment, as well as expert review for suspected sarcoma diagnoses.

At MD Anderson Cancer Center (MDACC), the grading of soft-tissue sarcoma uses histologic subtypes almost synonymously with the definition of grade in many cases. The following are high-grade by definition: UPS (formerly MFH), synovial sarcoma, pleomorphic liposarcoma, dedifferentiated liposarcoma, MPNST, rhabdomyosarcoma, epithelioid sarcoma, clear-cell sarcoma, alveolar soft part sarcoma, Ewing sarcoma, primitive neuroectodermal tumor, osteosarcoma, and mesenchymal chondrosarcoma. Intermediate-grade soft-tissue sarcomas include myxofibrosarcoma, myxoid liposarcoma, extraskeletal myxoid chondrosarcoma, and solitary fibrous tumor (hemangiopericytoma). Low-

grade soft-tissue sarcomas include well-differentiated liposarcoma. Grading for leiomyosarcoma, fibrosarcoma, and other unclassified sarcomas is determined individually by sarcoma pathologists on the basis of histologic morphology.

Staging and Outcomes

The American Joint Committee on Cancer (AJCC) staging system includes the most widely accepted soft-tissue sarcoma staging system in the world, and its eight edition of *Cancer Staging Manual* was recently published. It includes the following staging categories for soft-tissue sarcomas: histopathologic grade (G), tumor size (T), nodal involvement (N), and distant metastases (M). There is a significant change from seventh edition, that being to establish a functional system that can accurately stage the varied histologic entities that make up the compendium of diseases included under the umbrella of soft-tissue sarcoma. One of the most notable changes is that soft-tissue sarcomas are divided into the different staging systems by anatomic site, as follows: head and neck, extremity and trunk, abdomen/thoracic visceral organs, retroperitoneum, and other histologies/sites. In the eighth edition, T category criteria vary primarily by anatomic site, and the superficial versus deep distinction is eliminated. Prognostic stage grouping is also unique to each anatomic site category; however, the head/neck category and the abdomen/thoracic visceral organs category do not have stage grouping as insufficient data are available due to the fact that these are new categories. Nodal involvement (N1 disease), which is rare but associated with poor survival in soft-tissue sarcoma, is classified as stage IIIB in the retroperitoneal category, while it is classified as stage IV in the extremity/trunk category. Histologic grade (G1 to G3) continues to play an important role in soft-tissue sarcoma staging; the eighth edition utilizes the FNCLCC (Federation Nationale des Centres de Lutte Contre la Cancer) sarcoma grading system based on the histology-specific tumor differentiation score, mitotic count, and tumor necrosis. Of note, desmoid tumors/deep fibromatosis and Kaposi sarcoma remained excluded from the sarcoma staging system. GIST continues to have a unique staging system; it is now classified under the soft-tissue sarcoma section.

MDACC reported the results of a retrospective analysis of 1,225 patients with localized soft-tissue sarcoma treated with surgical resection and radiation therapy. By multivariate analysis, high-grade histology was a

risk factor for both local recurrence and distant metastases. The 5-year disease-specific survival rates were 96%, 87%, and 67% for low-, intermediate-, and high-grade tumors, respectively. The histologic subtypes rhabdomyosarcoma, epithelioid sarcoma, and clear-cell sarcoma were associated with shorter disease-specific survival (relative risk 1.6; 95% confidence interval [CI] 1.1 to 2.2; $p < 0.001$). Other risk factors for disease-specific survival included large tumor size (>5 cm), tumors located in the head/neck or deep trunk, age >64 years, and positive or uncertain margin status. Of note, rates of lymph node recurrence in this study were low (<3%) among all patients except for those with histologic subtypes of rhabdomyosarcoma (17% at 5 years), epithelioid sarcoma (18% at 5 years), and clear-cell sarcoma (15% at 5 years).

Multiple nomograms have been created to improve risk stratification of retroperitoneal sarcoma (RPS). MDACC published a postoperative nomogram for survival of patients with RPS, which was based on a retrospective analysis of 343 patients with RPS who underwent curative-intent surgery between 1996 and 2006. The nomogram incorporates the following factors: age (≥65 years), tumor size (≥15 cm), type of presentation (primary vs. recurrent), multifocality, completeness of resection, and histology. More recently, Gronchi et al. published a survival nomogram built on three cancer centers' data sets of RPS after primary resection. The analysis of 523 surgical patients with primary RPS revealed age, tumor size, grade, histologic subtype, multifocality, and extent of resection as prognostic factors for overall survival (OS). Their nomogram was validated in 135 patients from a fourth institution.

Presentation and Diagnosis

Clinical presentation of soft-tissue sarcoma depends on the anatomic site and depth of the tumor. Most extremity soft-tissue sarcomas present as an asymptomatic mass. Although a superficial tumor (e.g., back or hand tumors) becomes apparent when it is still small, a deeply located tumor (e.g., thigh tumors) can grow to 10 to 15 cm in diameter before it becomes apparent. RPSs generally present as a large mass (nearly 50% are larger than 20 cm when diagnosed) since they often do not produce symptoms until they are large enough to compress or invade contiguous structures. Occasionally, patients may present with neurologic symptoms resulting from lumbar or pelvic nerve compression or obstructive gastrointestinal symptoms.

Radiographic Evaluation

The goals of pretreatment radiologic imaging are to accurately define the local extent of a tumor and to exclude metastatic disease. Magnetic resonance imaging (MRI) has supplanted computed tomography (CT) as the imaging technique of choice for soft-tissue sarcomas of the extremities, except in patients in whom MRI is contraindicated. MRI accurately delineates muscle groups and distinguishes between bone, vascular structures, neurologic structures and tumor. In addition, sagittal and coronal views allow three-dimensional evaluation of anatomical compartments. A CT scan of the abdomen and pelvis should also be obtained in extremity myxoid liposarcomas because this disease is known to metastasize to the fatty tissue of the abdomen and retroperitoneum as well as to the axial skeleton.

For the vast majority of sarcomas, the predominant site of metastasis is the lung, and chest CT is used most often in patients with high-grade lesions to exclude metastatic disease. Specific radiologic evaluation of other areas can be indicated in certain histologies which have been shown to have unique patterns of metastatic spread. Examples of this include abdominal/retroperitoneal and bone imaging in patients with locally advanced extremity myxoid liposarcoma and brain imaging in patients with alveolar soft part sarcoma. In other sarcoma histologies, searches for bone and brain metastases are rarely indicated unless a patient has associated symptoms. A retrospective study of 1,170 patients with extremity soft-tissue sarcoma revealed that 10% had a distant metastasis at presentation, and 83% of these metastases were located in the lung. Among those patients with lung metastasis, 63% of metastases were detected by routine chest x-ray (CXR), whereas in 37%, the CXRs appeared to be normal. Higher risk of metastasis at presentation was observed in deep lesions (9% vs. 4%) and in high-grade tumors (11.8% vs. 7.0% in intermediate-grade and 1.2% in low-grade tumors). As for histologic subtypes, a higher risk of lung metastasis was observed in Ewing sarcoma (25%), MPNST (16%), extraskeletal chondrosarcoma (14%), and pleomorphic sarcoma (11%). The authors concluded that all patients with soft-tissue sarcoma should have a CXR, with chest CT reserved for patients with a suspicious lesion on CXR or for patients with a high-risk tumor (large tumor size [>5 cm], deep tumor location, or intermediate/high-grade histology).

CT remains the imaging technique of choice for RPSs. In addition to

giving invaluable information about anatomic considerations, radiologic subtleties between the various histologic types can be appreciated with CT. The role of positron emission tomography (PET) scan in patients with sarcoma has not been well defined. Many types of benign musculoskeletal tumors (e.g., Schwannoma) can show fluorodeoxyglucose F-18 (FDG) uptake in various degrees, making it difficult to establish the role of PET in the staging of patients with sarcoma.

Biopsy and Pathologic Evaluation

An accurate preoperative histologic diagnosis is critical in determining the primary treatment of a soft-tissue sarcoma. The biopsy should yield enough tissue so that a pathologic diagnosis can be made without increasing the risk of complications. Core-needle biopsy with or without fine-needle aspiration have been demonstrated to be reliable means of obtaining enough material for an accurate pathologic diagnosis, particularly when the pathologic findings correlate closely with clinical and imaging findings. Biopsy performed under ultrasound or CT guidance can improve the diagnostic accuracy. However, owing to heterogeneity within a tumor, sampling error can occur. Particularly in retroperitoneal liposarcomas, the failure to sample a nonlipogenic component of dedifferentiated liposarcoma can result in misdiagnosis. MDACC reported a retrospective study of 120 patients with retroperitoneal liposarcomas, which revealed that the overall subtype-specific diagnostic accuracy of percutaneous biopsy was 63%. The accuracy was especially lower in patients with dedifferentiated liposarcoma (36%), likely secondary to a sampling error and to the morphologic variability of dedifferentiated liposarcoma. Incorporating radiographic information into histologic assessment is important to improve diagnostic accuracy in patients with deep extremity or RPSs. One potential application for PET scan is for biopsy guidance. Many RPSs are heterogeneous and PET scan *may* help to identify the presence of a highly active component within the heterogeneous tumor. When percutaneous, image-guided biopsy is performed, the area identified as active on PET scan could be targeted.

Treatment Approach

The treatment of sarcomas requires a multidisciplinary approach. At MDACC, sarcoma cases are discussed regularly at multidisciplinary

conferences that include radiologists, pathologists, surgical oncologists, medical oncologists, and radiation oncologists. Preoperative chemotherapy and/or radiation therapy are used frequently in selected patients. Treatment strategies should be discussed in individual cases and should be based on a number of factors, most notably on tumor location, size, and histologic grade/subtypes. The overall principles of treatment include maximal locoregional control with complete surgical resection when possible, preoperative or postoperative radiation therapy, and/or chemotherapy.

Follow-Up

The rationale behind active follow-up strategies to detect recurrence in patients with soft-tissue sarcomas is that early recognition and treatment of recurrent disease can prolong survival. Extremity sarcomas most frequently recur as pulmonary metastases, whereas retroperitoneal or intra-abdominal sarcomas more commonly recur locally. Recurrence patterns also vary depending on histologic subtypes. The majority of soft-tissue sarcomas that recur do so within the first 2 years after the completion of therapy. Patients should therefore be examined every 3 months with chest imaging (as outlined previously) and primary site imaging during this high-risk period. Most experts recommend that the primary site be evaluated with either MRI for an extremity tumor or CT for intra-abdominal or retroperitoneal tumors. In some circumstances, ultrasonography can be used to look for local recurrence of an extremity tumor. Follow-up intervals may be lengthened to every 6 months, during years 2 through 5 after the completion of therapy. After 5 years, patients should be assessed annually, with chest and primary site imaging and physical examination.

EXTREMITY SOFT-TISSUE SARCOMAS

More than 50% of soft-tissue sarcomas originate in an extremity. The most common histologic subtypes include undifferentiated/unclassified sarcomas (previously MFH), liposarcoma, synovial sarcoma, and fibrosarcoma, although various other histologic types are also seen in the extremities.

Surgery

The mainstay of treatment is margin-negative surgical resection. The extent of surgical resection is based on tumor location, tumor size, depth of invasion, involvement of nearby structures, and the patient's performance status. In the 1970s, 50% of patients with extremity sarcomas were treated with amputation. However, despite a local recurrence rate of less than 10% after amputation, a large number of patients continued to die of metastatic disease. This realization led to the development of a consensus treatment algorithm consisting of limb-sparing surgical resection combined with postoperative radiation therapy. A landmark randomized trial from the National Cancer Institute by Rosenberg et al. in 1982 demonstrated no difference in survival among patients treated with limb-sparing surgery plus radiation therapy compared with patients treated with amputation. In 1985, on the basis of the limited data available, the National Institutes of Health developed a consensus statement recommending limb-sparing surgery for the majority of patients with high-grade extremity sarcomas. However, amputation remains the treatment of choice for patients whose tumor cannot be grossly resected with a limb-sparing procedure that preserves function (<5% of cases).

Radical, wide resection is the primary treatment of extremity sarcomas with ideally, a 2-cm margin, if possible. However, when this is not attainable (i.e., around neurovascular structures), surgeons should attempt to preserve major nerves since it is rare to have actual invasion into these structures. It is important to remember that there is generally a zone of compressed reactive tissue that forms a pseudocapsule around the tumors and that tumors may extend beyond this pseudocapsule. When possible, the biopsy site or tract should also be included en bloc with the resected specimen.

Before patients are referred to a specialized center, it is not uncommon for inexperienced surgeons to perform a suboptimal resection due to inadequate surgical planning. For these patients, re-resection is preferred if it can be achieved without functional compromise, in conjunction with either preoperative or postoperative radiation therapy. In cases where no radiologic or clinically evident tumor is apparent, in which re-resection would likely cause functional compromise, radiation therapy is an alternative option. At MDACC, among 666 patients who underwent apparent total tumor resection before presentation to MDACC without obvious macroscopic disease, 295 patients (44%) underwent re-resection. Among those who underwent re-resection, 136 (46%) patients had residual

tumor. The 5-year local control rates were 85% in the re-resection group and 78% in the non–re-resection group (p = 0.03), even though the re-resection group had a higher proportion of positive margins at pre-referral resection. Re-resection remained a significant predictor for improved survival after multivariate analysis.

Elective regional lymphadenectomy is rarely indicated in patients with soft-tissue sarcomas. However, in patients with histologies that carry a high risk of lymph node metastasis (such as rhabdomyosarcoma, epithelioid sarcoma, clear-cell sarcoma, and UPS), fine-needle aspiration or core needle biopsy should be performed of radiographically suspicious lymph nodes. In such cases, lymphadenectomy is recommended only if findings are positive. The role of sentinel lymph node biopsy in histologic subtypes susceptible to lymph node metastasis remains controversial. MDACC reported a retrospective study of 35 patients with synchronous (43%, n = 15) or metachronous (57%, n = 20) isolated nodal metastasis from extremity soft-tissue sarcomas who underwent lymphadenectomy. Epithelioid sarcoma (23%) and MFH (23%) were the most common histologic subtypes found to have lymph node metastases in this study, followed by clear-cell sarcoma (17%). The estimated 1-, 2-, and 5-year OS rates in patients with documented lymph node metastasis that underwent lymphadenectomy were 91%, 82%, and 60%, respectively. These outcomes more closely approximated the historical outcomes of patients with stage III disease (5-year OS 50%) compared to the 5-year OS of stage IV disease patients (25%), thus suggesting that aggressive surgical approaches, such as regional lymph node dissection in patients with confirmed lymph node metastasis, can have a positive impact on survival.

Multimodality Therapy

Radiation Therapy

The primary goal of radiation therapy is to optimize local tumor control. The evidence for adjunctive radiation therapy in patients eligible for limb-sparing surgical resection comes from two randomized trials and a number of large single-institution reports. In the late 1990s, two index randomized controlled trials were published favoring postoperative radiation therapy for patients with extremity soft-tissue sarcomas eligible for limb-sparing surgical resection. The study conducted at the National Cancer Institute randomized 91 patients with high-grade extremity tumors to limb-sparing surgery followed by chemotherapy alone or radiation therapy plus

postoperative chemotherapy. A second group of 50 patients with low-grade tumors were treated with resection alone versus resection with radiation therapy. The overall 10-year local control rates were 98% with radiation therapy versus 70% without radiation therapy, and improved local control rates with radiation therapy were seen in both of the high- and low-grade tumor cohorts. However, quality-of-life analysis showed that radiation therapy resulted in worse limb strength, edema, and range of motion, although these adverse effects were often transient and had little effect on daily activities.

In a second randomized trial conducted at Memorial Sloan Kettering Cancer Center (MSKCC), 164 patients were randomized to observation or brachytherapy (42 to 45 Gy) following limb-sparing surgery for extremity or resection of superficial trunk soft-tissue sarcomas. The 5-year local control rates were 82% in the brachytherapy group versus 69% in the no-brachytherapy group, respectively ($p = 0.04$). In subset analysis of the low-grade tumor cohort ($n = 45$), there was no benefit to brachytherapy in the local control ($p = 0.49$). There was no survival benefit observed in the radiation group in either study.

Brachytherapy

Brachytherapy, which involves the placement of multiple catheters in the tumor resection bed at the time of surgery, has been reported to achieve local control rates comparable to those achieved with external-beam radiation therapy. Guidelines have been established that recommend placing the afterloading catheters at 1-cm intervals with a 2-cm margin around the surgical bed. Usually, after the fifth postoperative day, the catheters are then loaded with radioactive wires (iridium-192) that deliver 42 to 45 Gy to the tumor bed over 4 to 6 days. The frequency of wound complications associated with brachytherapy is similar to that seen for postoperative radiation therapy (approximately 10%).

The primary benefit of brachytherapy is the shorter overall treatment time of 4 to 6 days, compared with the 4 to 6 weeks generally required by preoperative or postoperative external-beam radiation therapy regimens. Brachytherapy also produces less radiation scatter in critical anatomical regions (e.g., gonads, joints), with improved function a potential clinical benefit. Cost-analysis comparisons of brachytherapy versus external-beam radiation therapy have further shown that the charges for postoperative irradiation with brachytherapy are lower than those for external-beam

radiation therapy.

On the basis of the evidence from these studies, radiation therapy in conjunction with margin-negative surgery is recommended for patients with intermediate- to high-grade tumors to improve local control. Because T1 tumors (<5 cm) are less frequently associated with local recurrences, radiation therapy can be omitted in cases with low-risk of recurrence and wide margins (at least 1 cm). For low-grade tumors, radiation therapy can be considered in cases with positive or close margins (<1 cm).

Preoperative versus Postoperative Radiation Therapy

The optimal timing of radiation therapy for soft-tissue sarcomas remains a focus of active investigation. There are potential advantages in both preoperative and postoperative radiation approaches. In preoperative radiation therapy, the tumor itself displaces the normal structures and protects them from radiation exposure, which helps to limit the toxicity to surrounding normal structures. Additionally, the potential exists for radiation therapy to reduce tumor burden and enable a more limited, conservative surgical resection. The postoperative approach allows better histologic examination of resected specimens without distortion from treatment effect and is associated with fewer acute wound complications.

Currently, the only available randomized trial comparing preoperative and postoperative radiation therapy is a multicenter trial that was conducted in Canada, which randomized 190 patients with primary (90%) or recurrent (10%), mostly intermediate- or high-grade (83%) extremity soft-tissue sarcomas, to receive either 50 Gy of preoperative or 66 Gy of postoperative external-beam radiation therapy, in conjunction with limb-sparing surgical resection. Patients with positive margins in the preoperative group received a 16- to 20-Gy postoperative boost. This study was terminated at the interim analysis, due to a higher acute wound complication rate in the preoperative therapy group (35% vs. 17%, $p = 0.01$). In the update of this study with a median follow-up of 6.9 years, no significant differences were reported between the two groups in 5-year local control rates (93% in preoperative vs. 92% in postoperative therapy group) and 5-year OS rates (73% in preoperative vs. 67% in postoperative therapy group; $p = 0.48$). In regard to late toxicity, the study found a higher rate of grade 2 or greater fibrosis in the postoperative therapy group (48% vs. 32%; $p = 0.07$), which was associated with impaired function.

At MDACC, we favor the preoperative approach over the postoperative

approach for most patients with extremity soft-tissue sarcomas for several reasons. First, postoperative radiation therapy has a higher rate of late toxicity, which is usually irreversible (in contrast, acute wound complications are usually manageable and eventually heal). Second, lower doses and smaller field sizes can be used in the preoperative approach than in the postoperative approach. Third, rapidly improving radiation technologies, such as intensity-modulated radiation therapy (IMRT), are more effective in the preoperative setting, where the tumor can be precisely targeted and the radiation dose delivered to the surrounding structures can be minimized. This can be particularly important in preventing radiation damage to the joints. Finally, plastic surgery techniques that include advanced tissue transfer procedures are being used more frequently in patients with high-risk wounds, and this can achieve a high success rate (>90%) of healed wounds from a single-stage operation. The treatment strategy for extremity sarcomas treated at MDACC is summarized in Figure 5.3.

Chemotherapy

Despite improvements in the local control rate, metastasis and death remain significant problems for patients with high-risk soft-tissue sarcomas. This high-risk group includes localized sarcomas in nonextremity sites, tumors which show an intermediate- or high-grade histology, or large (T2) tumors. The treatment regimen for patients with high-risk localized disease, metastatic disease, or both, usually includes chemotherapy. Systemic chemotherapy is a particularly important component of several sarcomas that occur predominantly in children, such as rhabdomyosarcoma, Ewing sarcoma, and osteogenic sarcoma. It is also well recognized that myxoid liposarcoma and synovial sarcoma are chemosensitive soft-tissue sarcomas.

Only three drugs, doxorubicin, dacarbazine, and ifosfamide, have consistently achieved response rates of at least 20% as single-agent treatments in patients with advanced soft-tissue sarcomas. The majority of active chemotherapeutic trials have included doxorubicin as part of the treatment regimen. The response rate to ifosfamide has been found to vary from 20% to 60% in single-institution series in which higher-dose regimens have been used or in which ifosfamide was given in combination with doxorubicin. Recently, several agents have been FDA approved for patients with metastatic sarcoma. Trabectedin, a DNA-binding agent is

approved for patients with liposarcoma or leiomyosarcoma. Eribulin is a microtubule inhibiting agent approved in the treatment of liposarcoma. Olaratumab is a monoclonal antibody blocking the PDGFR-α receptor that has recently (11/2016) been approved in combination with doxorubicin in any adult soft-tissue sarcoma histology that would be appropriately treated with an anthracycline-containing regimen.

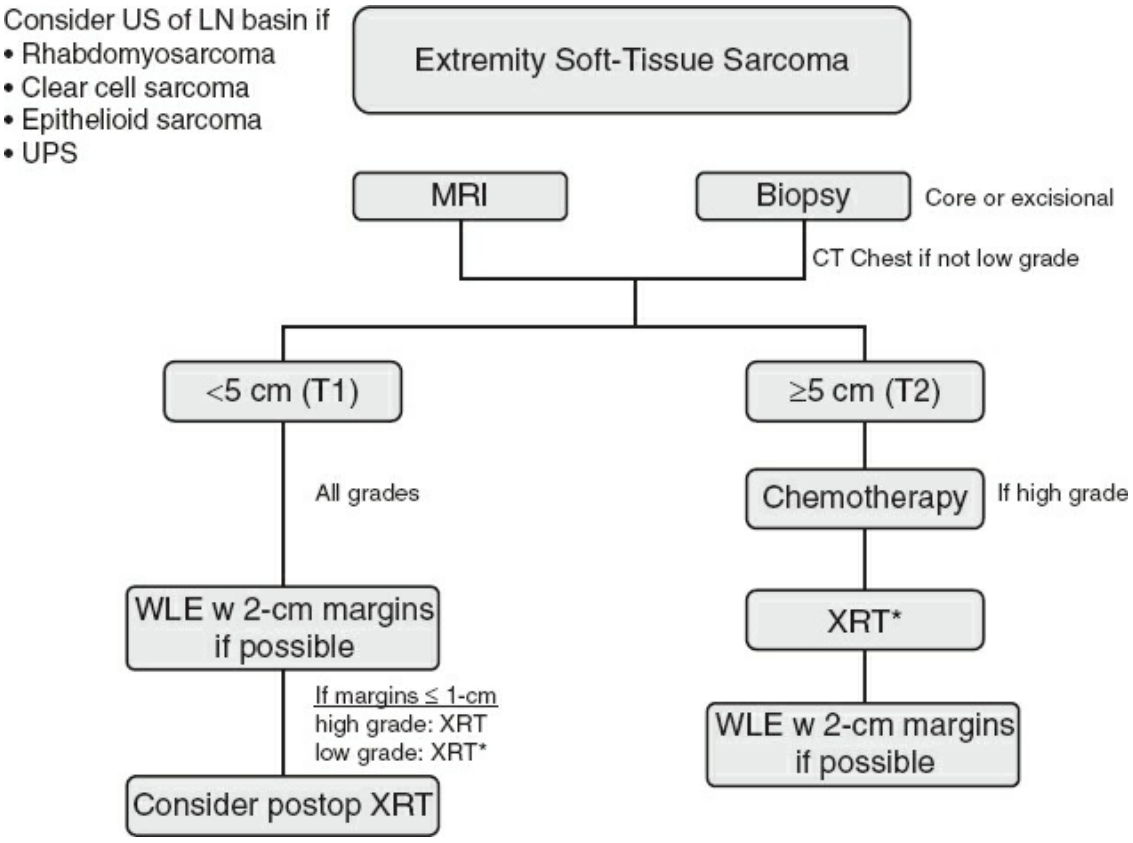


Figure 5.3 Treatment strategy for extremity soft-tissue sarcomas. *Low grade: XRT reserved for selected patients with recurrent or deeply infiltrative primary. US, ultrasound; LN, lymph nodes; CT, computed tomography; MRI, magnetic resonance imaging; UPS, unclassified pleomorphic sarcoma.

Postoperative Chemotherapy

Individual randomized trials of postoperative chemotherapy have failed to demonstrate an improvement in disease-free or OS in patients with soft-tissue sarcomas. However, there are several criticisms of these individual trials that may explain why they failed to demonstrate improvement in survival. First, the chemotherapy regimens used were suboptimal, in that single-agent drugs (most commonly doxorubicin) were studied and dosing schedules were less intensive. Second, the sample sizes in these trials were

not large enough to allow the detection of clinically significant differences in survival. Third, the majority of patients who did not respond to the initial treatment regimen were started on other chemotherapeutic regimens that potentially affected disease-free and OS. Finally, most studies included patients at low risk for metastasis and death, that is, those with small (<5 cm) and low-grade tumors.

Hence, the role of postoperative chemotherapy in soft-tissue sarcomas has been controversial. The first randomized trial of postoperative chemotherapy for soft-tissue sarcomas was conducted at MDACC in 1973 and showed improved disease-free survival in the chemotherapy cohort. Since then, multiple randomized trials have been conducted with conflicting results. A formal meta-analysis was conducted by the Sarcoma Meta-Analysis Collaboration in 1997; this group analyzed data from 1,568 patients in 14 trials of doxorubicin-based postoperative chemotherapy to determine the effect of postoperative chemotherapy on localized, resectable soft-tissue sarcomas. In this trial, with a median follow-up of 9.4 years, doxorubicin-based chemotherapy significantly lengthened the time to local and distant recurrence and the overall recurrence-free survival. There was a trend toward improved OS in the postoperative therapy group (HR for death 0.89, 95% CI 0.76 to 1.03; $p = 0.12$), but the absolute benefit at 10 years was only 4%. The same group updated the analysis by adding several subsequent randomized trials. The results from the updated analysis of data from 18 trials, which included 1,953 patients, were similar to those of the earlier analysis; however, it showed that the use of doxorubicin combined with ifosfamide was associated with improved OS (OR 0.56, 95% CI 0.36 to 0.85; $p = 0.01$), with absolute risk reduction of 11% (41% vs. 30%) (Table 5.2). Based on these analyses, a chemotherapy regimen including ifosfamide is generally recommended.

TABLE 5.2 Meta-Analysis of Adjuvant Chemotherapy for Soft-Tissue Sarcoma (Sarcoma Meta-Analysis Collaboration, 2008)

Outcomes	No. of Trials	No. of Patients	Odds Ratio (95% CI)	*P* value	Absolute risk Reduction (%)
Local recurrence	17	1,700	0.73 (0.56–0.94)	0.02	3
Distant recurrence	18	1,747	0.69 (0.56–0.86)	0.001	9
Overall recurrence	18	1,747	0.67 (0.56–0.82)	0.0001	10
Overall survival (All regimens)	18	1,953	0.77 (0.64–0.93)	0.01	6
Overall survival (Doxorubicin-based + Ifosfamide)	5	414	0.56 (0.36–0.85)	0.01	11

However, the use of postoperative chemotherapy for resectable soft-tissue sarcomas remains controversial. The above-mentioned meta-analyses did not include the most recent two largest randomized trials conducted by the European Organisation for Research and Treatment of Cancer (EORTC). These studies tested doxorubicin/ifosfamide-containing regimens. The pooled analysis of a total of 819 patients from these two studies showed that postoperative chemotherapy was associated with improved recurrence-free survival (HR 0.74, 95% CI 0.60 to 0.92; p = 0.006), but not with OS.

Preoperative Chemotherapy

The potential advantages to preoperative chemotherapy over a postoperative approach include tumor reduction (which may enable more limited resection), early treatment of potential micrometastases, patient selection for surgery in cases with borderline resectable tumors or tumors with questionable metastases, and most importantly, in vivo evaluation of treatment effectiveness. Given that only 30% to 50% of patients respond to standard chemotherapeutic regimens, a preoperative approach enables the oncologist to identify patients who respond to specific regimens, as shown radiographically and pathologically. Treatment responders after two or four courses of chemotherapy subsequently undergo surgery, often after preoperative radiation therapy, and then continue postoperative chemotherapy with the same agents that are known to be effective for them. Moreover, patients who did not respond to short courses of preoperative chemotherapy can be spared the toxic effects of prolonged postoperative chemotherapy with agents to which the tumor is insensitive.

Currently, there is no evidence available from phase III randomized controlled studies to define the role of preoperative chemotherapy in soft-tissue sarcomas. A retrospective analysis of 356 patients with high-grade extremity soft-tissue sarcomas conducted at MSKCC showed that preoperative chemotherapy (doxorubicin plus ifosfamide) improved disease-specific survival compared with survival in the surgery-alone cohort (HR 0.52, 95% CI 0.30 to 0.92; $p = 0.02$) after stratification by size, histology, and age. The authors concluded that preoperative chemotherapy is beneficial in patients with high-grade extremity soft-tissue sarcomas >10 cm. The EORTC group conducted a phase II study that randomized 150 patients with high-risk soft-tissue sarcomas (approximately 80% of which were located in extremities) to a preoperative chemotherapy (doxorubicin plus ifosfamide, three cycles) group versus a local treatment—only group. Postoperative radiation therapy was indicated based on margin status (<1 cm) irrespective of the study arm; 46% in the chemotherapy group and 54% in the local treatment—only group received radiation therapy. This study was closed before expansion into a phase III trial due to its slow accrual. Although the study was underpowered, precluding definitive conclusions, it failed to show a survival benefit in those receiving preoperative chemotherapy; the 5-year OS rates were 64% in the local treatment—only group and 65% in the chemotherapy group ($p = 0.22$).

A cohort analysis of the combined databases from both MDACC and MSKCC was performed evaluating the efficacy of chemotherapy in high-grade soft-tissue sarcomas. The data on 674 patients with stage III extremity sarcoma who received either preoperative or postoperative doxorubicin-based chemotherapy were reviewed to determine their outcomes (5-year disease-specific survival, as well as 5-year local and distant recurrence rates). The 5-year disease-specific survival rate was 61%, and the probability of local and distant recurrences at 5 years was 83% and 56%, respectively. An important conclusion from this study was that the clinical benefits of doxorubicin-based chemotherapy in patients with high-risk extremity sarcomas were not sustained beyond 1 year after therapy. The investigators then went on to compare their study with the Sarcoma Meta-Analysis Collaboration and made the following observations. First, the patient population of the Sarcoma Meta-Analysis Collaboration was more heterogeneous than that of the cohort study, in that it included patients with both primary and recurrent extremity and nonextremity sarcomas. Second, there were also fewer uncontrolled

variables in the cohort study. On the basis of these findings, the authors urged caution when reviewing studies of chemotherapeutic regimens with a short-term follow-up and concluded that there remains no consensus regarding the role of chemotherapy in patients with localized high-risk soft-tissue sarcomas.

As seen with outcomes, response rates to chemotherapy are likely related to histologic subtype. Certain subtypes of sarcoma have been shown to be more chemosensitive, such as synovial sarcoma. Eilber et al. from MSKCC reported a retrospective review of prospectively collected data of 101 patients with T2b extremity synovial sarcoma who underwent surgical resection. Sixty-seven percent of patients received ifosfamide-based therapy (85% preoperatively), which was associated with improved disease-specific survival (4-year, 88% vs. 67%; $p = 0.01$). The same group also reported a retrospective study of 245 patients with T2 high-grade extremity liposarcomas who underwent surgical resection. Approximately half (49%) of the patients had myxoid/round cell, 40% had pleomorphic, and 11% had dedifferentiated subtype of liposarcoma. Sixty percent of patients received pre- or postoperative chemotherapy (doxorubicin-based [34%] or ifosfamide-based [26%]). Ifosfamide-based chemotherapy was found to be associated with improved survival (5-year disease specific survival, 92% vs. 65%; $p < 0.001$), whereas doxorubicin-based chemotherapy was not.

At MDACC, we prefer the preoperative approach based on available data and the above-described theoretical advantages. Our standard treatment algorithm is described in Figure 5.3. We often use preoperative chemotherapy followed by radiation therapy in patients with large (T2) high-grade tumors. Future studies are warranted to determine the survival benefit of this approach and to define the most effective regimen.

Isolated Limb Perfusion Therapy

While limb salvage has become possible for the majority of patients with soft-tissue sarcomas, it is not feasible in approximately 5% of patients. Regional therapy with isolated limb perfusion (ILP) or isolated limb infusion (ILI) has been evaluated in patients with advanced sarcoma for limb preservation. One of the largest series from the Netherlands used ILP with tumor necrosis factor-α (TNF-α) and melphalan in 217 patients with soft-tissue sarcomas. The reported response rate was 75% and a limb salvage rate of 87%. ILI, as an alternative method of regional

chemotherapy, seems equally as efficacious. The Sydney Melanoma Unit reported a response rate of 90% in 21 patients with sarcoma using ILI including 65% of patients with a complete response; however, the recurrence rate in this study, with a median follow-up of only 28 months, was 42%. It is important to note that these studies included infusion of TNF-α, which is not available in the United States. As expected, it is difficult at this stage to interpret results for this technique since the data available represent a small population with heterogeneous histologies in which a variety of chemotherapeutic agents and indications have been used.

Management of Local Recurrence

Disease can recur in up to 20% of patients with extremity sarcoma, typically within 2 years after resection. Local recurrence is associated with shorter survival, although whether local recurrence is causative for shorter survival or is a marker of aggressive disease is controversial. Regardless, the adequacy of the surgical resection clearly plays a significant role in determining whether the disease recurs locally.

An isolated local recurrence should be treated aggressively by complete resection with a wide margin (10% to 20% of patients require amputation due to vital structure involvement) plus radiation therapy, commonly delivered preoperatively (for the reasons previously discussed) at MDACC. The use of preoperative or postoperative chemotherapy is determined on a case-by-case basis. Several small studies have shown that patients with isolated local recurrences may be successfully retreated, with local recurrence-free survival rates approaching 72%. Treatment for patients who received previous irradiation can be complicated, since repeat irradiation increases complications such as impaired wound healing, osteonecrosis, and fibrosis, which can even result in future amputation due to these complications. However, simple wide resection harbors a high risk of local control failure, and amputation remains an option to provide adequate local control. Patients may be considered for brachytherapy or intraoperative radiation therapy. Use of plastic surgery techniques such as rotational tissue flaps is encouraged to enable more radical resection and improve wound healing.

We reported our experience in managing local recurrence in patients who had received previous irradiation at MDACC. Of 62 patients in this study, 25 had undergone resection alone, whereas 37 had received

postoperative radiation therapy (33 receiving brachytherapy) after resection. Local control rate at 5 years was 51%. On multivariate analysis, positive margins were associated with higher risk of local failure. Postoperative radiation therapy did not improve the local control rate (5-year rates: 58% in the radiation group vs. 39% in the surgery-only group; $p = 0.4$) or disease-specific survival (5-year rates, 66% vs. 67%; $p = 0.8$). The wound complication rate was significantly higher in the irradiation group (80% vs. 17%, $p < 0.001$). Interpretation of these results is difficult because of selection bias; however, treating physicians need to be aware of the risk associated with re-irradiation in patients with recurrent soft-tissue sarcoma.

Management of Distant Disease

Distant metastases occur in 40% to 50% of patients with intermediate- and high-grade extremity sarcomas. Most metastases to distant sites occur within 2 years of the initial diagnosis, and the predominant site of distant metastases from primary extremity sarcomas is the lung (>70%). The mainstay of treatment for metastatic disease is systematic chemotherapy, but metastasectomies can improve survival for selected patients.

Isolated lung metastases should be considered for resection if there are no extra pulmonary metastases, the patient is medically fit enough to withstand surgery, and the lesions are amenable to resection. Large series have revealed 3-year survival rates of 40% to 50% in patients with completely resected pulmonary metastases. A disease-free interval of more than 12 months, the ability to resect all metastatic disease, age younger than 50 years, and the absence of preceding local recurrence were found to be independent prognostic factors in a multivariate analysis of patients who underwent resection of pulmonary metastases.

Extremity Sarcomas, General Recommendations (Fig. 5.3)

1. Soft-tissue tumors that are enlarging or greater than 3 cm in diameter should be evaluated with radiologic imaging (ultrasonography, CT, or MRI), and a tissue diagnosis made on the basis of core-needle biopsy findings.
2. Evaluation for metastatic disease once a sarcoma diagnosis is established: chest radiography for low- or intermediate-grade lesions

and T1 tumors, and chest CT for high-grade or T2 tumors.

3. A wide local excision with 2-cm margins is adequate therapy for low-grade lesions and T1 tumors.
4. Radiation therapy plays a critical role in the management of T2 tumors.
5. Patients with recurrent high-grade sarcomas or distant metastatic disease should be considered for preoperative or postoperative chemotherapy.
6. An aggressive surgical approach should be taken in the treatment of patients with an isolated local recurrence or resectable distant metastases.

RETROPERITONEAL SARCOMAS

Among soft-tissue sarcomas in adults, 15% to 20% occur in the retroperitoneum. Most retroperitoneal tumors are malignant, and approximately one-third are soft-tissue sarcomas. The differential diagnosis in a patient presenting with a retroperitoneal tumor includes lymphoma, germ cell tumors, and undifferentiated carcinomas. The most common RPSs are liposarcomas (50% to 65%, mainly well-differentiated or dedifferentiated liposarcomas), leiomyosarcomas (20% to 25%), and undifferentiated/unclassified sarcomas (previously categorized as MFH). Reported histologic frequencies in RPSs vary across studies; despite this, histology remains a key component to overall prognosis. Analysis of an MDACC database of 1,118 patients with RPSs revealed dramatic differences in behavior among the three subgroups of histologies (well-differentiated liposarcoma, other liposarcomas [mostly dedifferentiated liposarcoma], and other histologies [mainly leiomyosarcoma and undifferentiated/unclassified sarcomas]); 5-year OS rates were 95% in well-differentiated liposarcoma, 25% in other liposarcomas, and 43% in other histologies ($p < 0.001$). The importance of histologic subtypes in predicting tumor behavior and survival was also reported by two more recent large retrospective studies from MSKCC and the European Multi-Institutional Collaborative RPS Working Group. Based on these reports, liposarcoma has a high local recurrence rate (35% to 60%) and high metastasis rate if dedifferentiated (30%), whereas leiomyosarcoma has a higher distant metastasis rate (60%) and a low local recurrence rate (<20%). These two most common subtypes of RPS have characteristics distinct from each other. Treatment strategies should be individualized on

the basis of tumor histology by dedicated multidisciplinary specialists in sarcoma.

Clinical Presentation

RPSs generally present as large masses; nearly 50% are larger than 20 cm at the time of diagnosis. They typically do not produce symptoms until they grow large enough to compress or invade contiguous structures. On occasion, patients may present with neurologic symptoms, resulting from the compression of lumbar or pelvic nerves, or obstructive gastrointestinal symptoms, resulting from the displacement or direct tumor involvement of an intestinal organ.

Evaluation

The workup of a patient with a retroperitoneal mass begins with an accurate history that should exclude signs and symptoms of lymphoma (e.g., fever, night sweats). A complete physical examination with particular attention to all nodal basins and a testicular examination in males are critically important. Laboratory assessment can be helpful; an increased lactate dehydrogenase level can be suggestive of lymphoma, whereas an increased β-human chorionic gonadotropin level, alpha-fetoprotein level, or both can indicate a germ cell tumor.

The radiologic assessment should include a CT scan of the abdomen and pelvis to define the extent of the tumor and its relationship to surrounding structures, particularly vascular structures. Imaging should include the liver in a search for metastases and discontinuous abdominal disease. The kidneys should also be evaluated to assess bilateral renal function. Thoracic CT is indicated to look for lung metastases in patients with high-grade tumors. A CT-guided core-needle biopsy is appropriate for obtaining a tissue diagnosis in patients presenting with an equivocal history, an unusual-appearing mass, an unresectable tumor, or distant metastasis and in patients who are potentially eligible for preoperative therapy.

Surgery

Complete surgical resection is the mainstay of treatment for primary RPSs. Wide, negative margins are frequently not possible due to anatomic constraints. In several retrospective assessments of patients with RPSs,

complete surgical excision (R0 or R1) was achieved in only 40% to 60% of patients. Incomplete or debulking (R2) resection may improve local symptoms but does not improve survival.

The quality of surgical resection is important for outcomes. First, margin-positive resection increases the chance of local recurrence. This is vital since local recurrence is often the cause of mortality in RPS. This has been shown by MDACC in a study of 83 patients treated with surgery and radiotherapy. Five-year local control rates were 33% after a margin-positive resection versus 62% after margin-negative resection ($p = 0.01$). This study further highlights the importance of local recurrence in that of the 38 patients dying of disease, local recurrence was the sole site of disease in 16 (42%) patients and was a component of progression in an additional 11 (29%). Second, incomplete resection has also been associated with a risk of developing distant metastasis that is almost four times higher than in those who undergo complete resection. Finally, it has an important impact on survival. In an analysis of 500 patients with RPS treated at MSKCC, the median survival duration of patients who underwent complete resection was 103 months versus 18 months for patients who underwent incomplete resection, which was no different than the survival seen in patients treated with observation without resection, thus demonstrating that there is no survival benefit from debulking procedures.

Careful preoperative planning is of paramount importance when considering surgical resection. Multiorgan resection is often required to achieve complete resection. Multidisciplinary surgical teams are frequently necessary, such as vascular surgery, when resection and/or reconstruction of great vessels are required.

How extensive the surgical resection should be is an area of active controversy. Extrapolating the treatment concept of “extended or compartmental resection” from the treatment algorithm for extremity sarcomas to the treatment of RPSs, would potentially result in the resection of uninvolved adjacent organs. In a French retrospective study of 382 patients with RPSs reported by Bonvalot et al. in 2009, nephrectomy was performed in 42% and colectomy in 30% of patients. The local recurrence rate was 44%. The authors advocated for compartmental resection which was associated with improved local control (a 3.29 times lower rate of local recurrence than with simple complete resection). There was no improvement in OS in patients treated with such an approach. Moreover, a

high surgical complication rate of 16% was reported; in half of these patients, further surgery was required to manage complications. Thirteen patients (3%) died perioperatively from surgical complications, and 3 (1%) died intraoperatively in this study.

Gronchi et al. from an Italian group evaluated the impact of compartmental resection compared to "standard" resection based on a change in institutional surgical "philosophy" over time. This study divided patients into two groups by time period, before and after the concept of extended resection was employed into practice. After such an approach was introduced, there was an associated improvement in the local recurrence rate from 48% to 28% (p = 0.007); however, the distant metastasis rate increased from 13% to 22% (p = 0.013), with no statistically significant change in OS (5-year rates, 51% vs. 60%; p = 0.47). Moreover, because of the nature of this design, patients in the extensive resection group had significantly shorter follow-up (almost half), which may contribute to the differences in local recurrence.

Limitations of the extended or "compartmental resection" approach have hindered its adoption into clinical practice. RPSs are usually large, abutting multiple organs in all directions. Multi-visceral resection, although often necessary, significantly increases the morbidity and mortality associated with resection, likely in an exponential fashion. This makes it difficult to justify the resection of uninvolved "adjacent" organs (e.g., kidney, pancreas, duodenum). Therefore, it is our practice to resect adjacent structures with evidence of invasion, either radiographically or at the time of surgical exploration. Structures that are clearly not invaded by the tumor are preserved (Fig. 5.4).

Multimodality Therapy

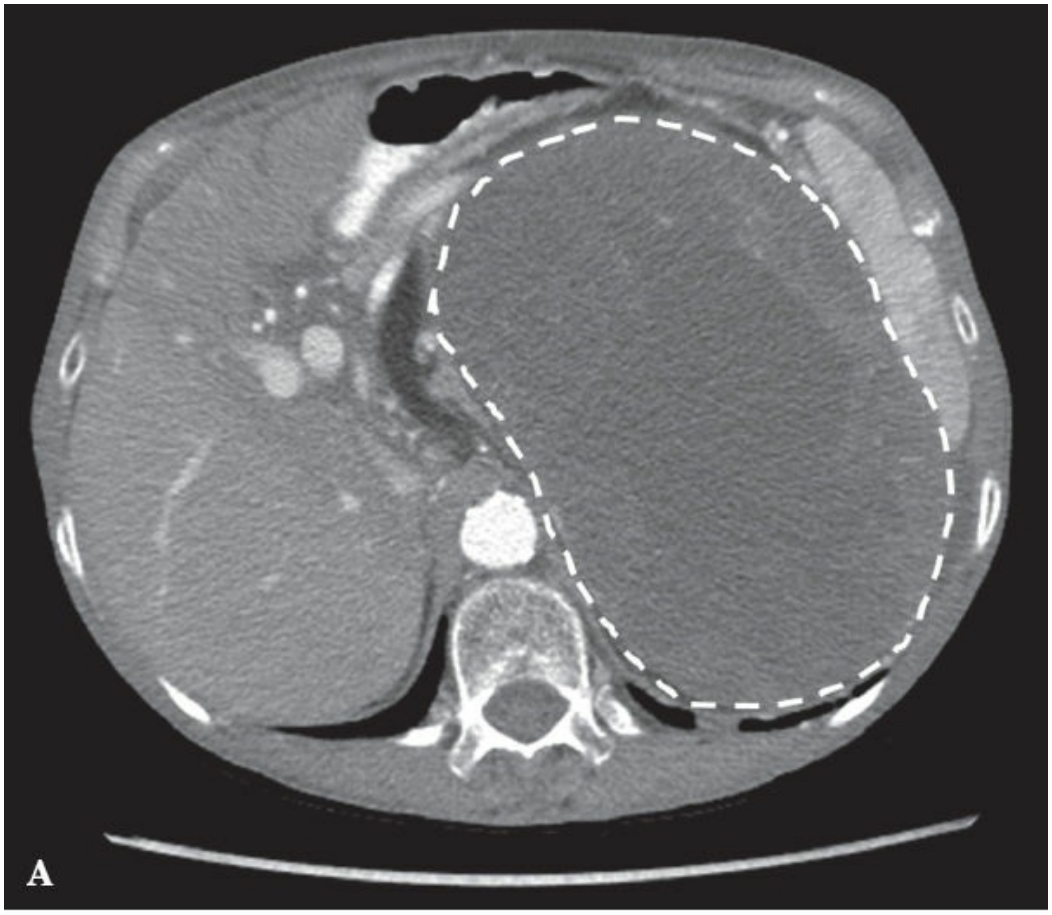
The high local and distant recurrence rates in RPS have resulted in a shift in treatment strategies for localized RPS toward multimodality therapy, such as perioperative use of chemotherapy and/or radiation therapy. Because of the rarity of RPSs, there is no level I evidence conclusively supporting the role of radiation or chemotherapy for localized RPS. Perioperative use of chemotherapy or radiation therapy has been used in RPS to improve outcome, mainly based on data from limited retrospective studies of RPS patients and on data extrapolated from extremity sarcoma cases, as described in earlier sections.

Radiation Therapy

Several retrospective studies have reported the benefits of postoperative radiation therapy. However, it is often difficult to deliver radiation therapy to RPSs postoperatively, even with advanced techniques such as IMRT, because the bowel and other organs are frequently located in the resected area.

The current trend for treating RPSs with radiation therapy is a preoperative approach, as the tumor often displaces adjacent radiosensitive organs. Using IMRT, preoperative radiation therapy is believed to minimize radiation exposure to normal structures while allowing focused irradiation of the tumor (Fig. 5.5).

Researchers from MDACC and colleagues from Toronto reported data from two prospective trials that examined the effects of preoperative radiation therapy in RPS. A total of 72 patients with intermediate- or high-grade RPS (40% liposarcoma, 26% leiomyosarcoma, and 15% MFH) were treated with preoperative radiation therapy. Only two patients (3%) did not complete the planned radiation dose, which supported the feasibility of the preoperative approach. Despite the inclusion of only high-risk patients, this study achieved favorable outcomes with a 5-year local recurrence-free survival rate of 60% and a 95% complete resection rate.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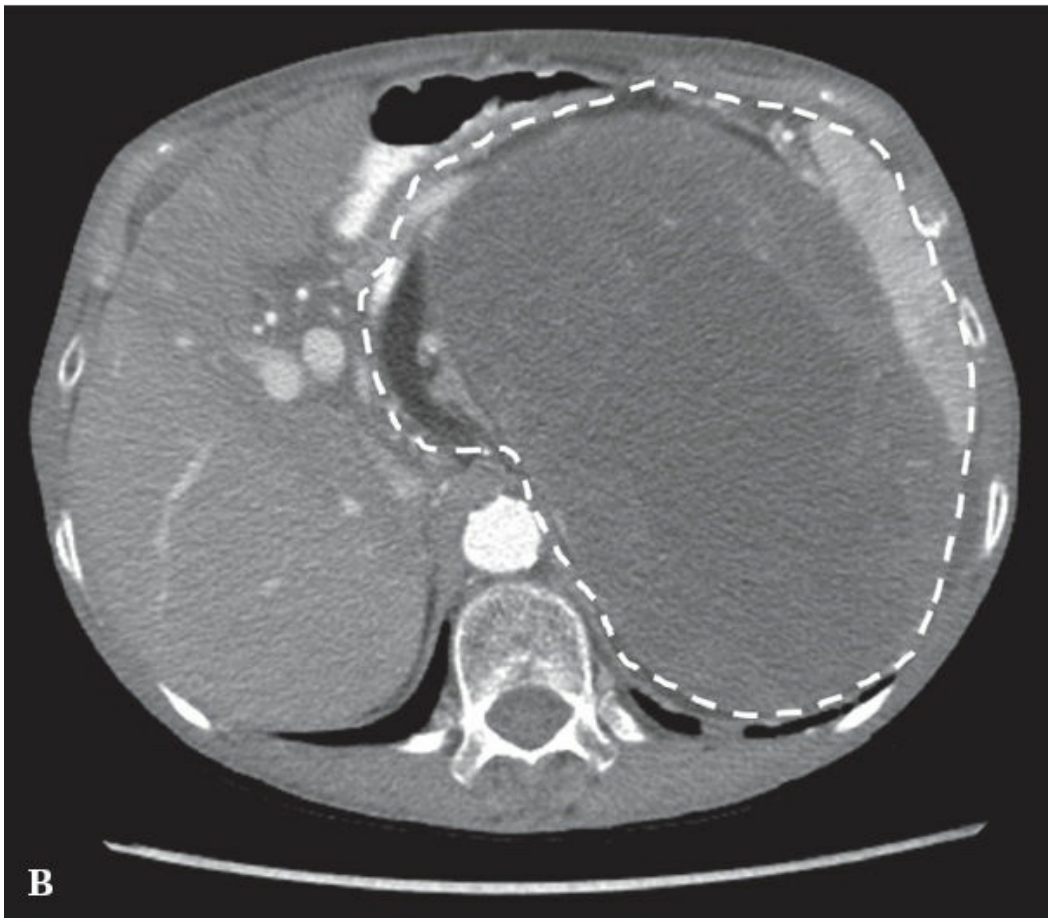
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Figure 5.4 Cross-sectional imaging demonstrating the extent of resection by (**A**) a traditional organ-sparing resection as compared to (**B**) extended "compartmental" resection. Margin status of resection would be limited at the level of the aorta, the spine, and the body wall, regardless of extent of resection.

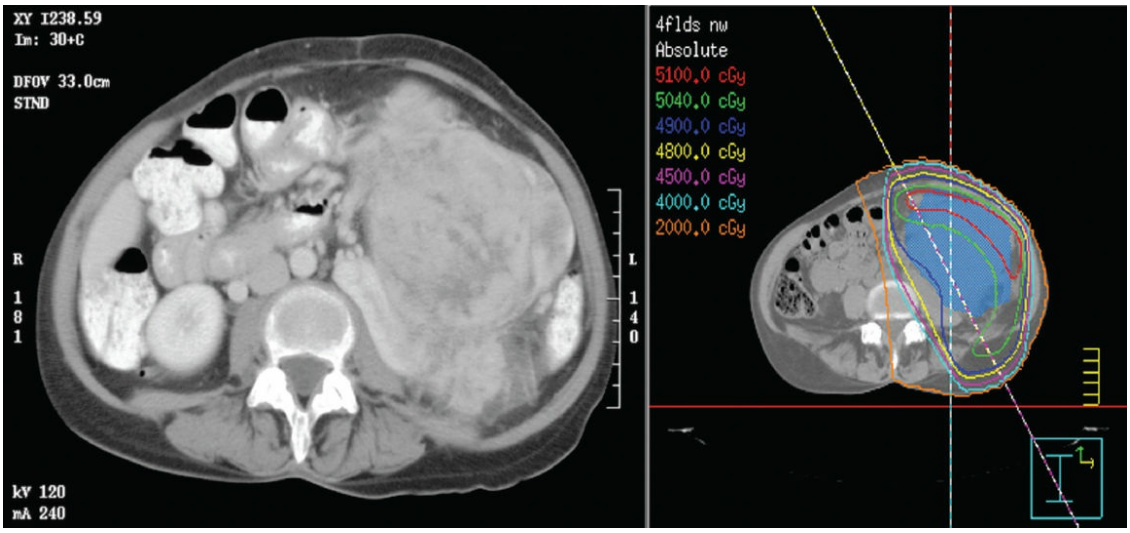

Figure 5.5 Imaging of intensity-modulated radiation therapy planning, targeting a large retroperitoneal sarcoma.

Another consideration includes a combined approach of preoperative radiation therapy with intraoperative radiation. Stucky et al. from the Mayo Clinic-Arizona reported the results of a retrospective study of 63 patients (37 who underwent preoperative radiation, surgery, plus intraoperative radiation and 26 who had surgery alone). Radiation therapy was associated with an improved 5-year local control rate (89% vs. 46% in the surgery-alone group; $p = 0.03$), which remained significant after multivariate analysis. There was no impact on OS.

Postoperative brachytherapy has not been shown to be effective in combination with preoperative radiation therapy. Smith et al. reported the long-term follow-up of a phase II trial of 40 patients with RPS who had received preoperative radiation therapy with or without postoperative brachytherapy. The additional brachytherapy was associated with an unacceptable toxicity profile, typically associated with duodenitis/duodenal stricture and death. Neither recurrence-free survival nor OS was improved in patients who received additional brachytherapy.

Nussbaum et al. recently reported the results of propensity score-matched analyses of patients with RPS from the National Cancer Data Base. This study compared 563 patients who received preoperative or

2,215 patients who received postoperative radiation therapy, to 6,290 patients who had no radiation therapy. This study showed that radiation therapy, either by the preoperative or postoperative approach, improved OS compared with surgery alone (preoperative: HR 0.7, 95% CI 0.59 to 0.82; $p < 0.70$; postoperative: HR 0.78, 95% CI 0.71 to 0.85; $p < 0.001$).

Currently, the EORTC is conducting a prospective randomized phase III study (EORTC 62092, STRASS trial; NCT01344018) comparing preoperative radiation (50.4 Gy in 28 fractions) plus surgery to surgery alone. When this trial is completed, it may better define the role of preoperative radiation therapy in RPS. Results are expected in 2020.

Chemotherapy

Data on postoperative or preoperative chemotherapy in RPS are very limited. Recently, a group from the Medical College of Wisconsin reported data from the National Cancer Database. Of 8,653 patients with surgically resected RPS, 1,525 (18%) received either preoperative (11%) or postoperative (7%) chemotherapy. Patients with tumors classified as intermediate/high-grade, leiomyosarcoma, or UPS histology and R2 resection status received chemotherapy more frequently. After propensity score matching, the median OS was shorter in patients who received chemotherapy (40 vs. 52 months; $p = 0.002$). Two other similar retrospective studies, reported by Singer et al. in 1995 and Bremjit et al. in 2014, showed adverse outcomes associated with postoperative or preoperative chemotherapy in RPS; however, because of innate selection bias associated with these retrospective studies, it is difficult to definitively assess the role of chemotherapy in RPS.

MDACC reported the safety of preoperative chemotherapy in a retrospective study of 309 patients with primary soft-tissue sarcomas, including 108 located in retroperitoneum/viscera. Preoperative chemotherapy did not increase surgical complication rates in patients with RPS (29% vs. 34% in the upfront surgery group; $p = 0.66$). MDACC also evaluated the impact of radiographic response to preoperative chemotherapy on the extent of surgical resection. In this retrospective study of 65 patients with stage II or III sarcoma (23 retroperitoneal) who were treated with preoperative chemotherapy, the radiographic response was sufficient to decrease the extent of surgery in 13%. Patients with a radiographic response had a higher negative-margin resection rate, a better local recurrence-free survival rate, and a better OS rate than did

nonresponders.

Our practice is to determine treatment strategies for individual patients with RPS at a multidisciplinary sarcoma conference. We carefully use preoperative chemotherapy and/or radiation therapy, typically in patients with soft-tissue sarcomas that are at high risk of distant metastasis, such as intermediate- or high-grade histology and large or recurrent tumors. Pretreatment biopsy and histologic confirmation are mandatory before initiating any preoperative therapy for RPS. The most commonly used regimen is doxorubicin plus ifosfamide, which is supported by data extrapolated from studies of extremity soft-tissue sarcomas. The preoperative approach is preferred for several reasons, which were described in the previous section. In addition to the previous considerations, in patients with RPS that involve the kidney, preoperative multidisciplinary planning is critical as administration of ifosfamide requires two kidneys due to potential nephrotoxicity.

Targeted Therapy

The development of targeted therapies may improve the efficacy of systemic therapy for soft-tissue sarcomas in the future. One such therapy being investigated is inhibitors of CDK4, a cyclin-dependent kinase frequently overexpressed in liposarcomas. Dickson et al. from MSKCC recently published the results of a phase II trial of a CDK4 inhibitor administered to 60 patients with liposarcomas (47 dedifferentiated and 13 well differentiated). They reported one complete response lasting more than 2 years. The overall progression-free survival at 12 weeks was 57%. MDM2 inhibitors for treatment of liposarcomas are also being investigated.

Treatment for Recurrent Disease

RPSs recur following complete surgical resection, in two-thirds of patients. In addition to recurring locally in the tumor bed and metastasizing to the lungs, retroperitoneal leiomyosarcomas frequently spread to the liver and soft tissues. RPSs can also recur diffusely throughout the peritoneal cavity (sarcomatosis). Not only does each local recurrence affect surgical therapy, it can also be associated with a change in the biology of the disease. For example, in as many as 25% of patients, well-differentiated liposarcoma may recur in a poorly differentiated form or develop areas of dedifferentiation. Dedifferentiated retroperitoneal liposarcoma is more

aggressive with a greater propensity for distant metastasis than its well-differentiated precursor.

The approach to resectable recurrent disease after the treatment of an RPS is similar to the approach taken after the recurrence of an extremity sarcoma. However, the ability to adequately resect a recurrent RPS declines precipitously with each recurrence. A survival benefit of salvage surgery for recurrent RPS has been reported, but careful patient selection is critical.

Park et al. from MSKCC reported the results of a retrospective analysis of 105 patients with a first recurrent retroperitoneal liposarcoma, 61 of whom underwent salvage resection. The size and growth rate of the recurrent tumor were independently associated with the incidence of a second local recurrence. A recurrent tumor with a growth rate >0.9 cm/month was associated with a poorer outcome, and the authors concluded that patients with tumors such as these should be enrolled in clinical trials rather than undergo re-resection.

Resection of metastatic lesions also can be considered in selected patients. For example, patients with leiomyosarcoma have been reported to have a better survival after resection of distant metastasis as compared to other subtypes; therefore patients with distantly recurred retroperitoneal leiomyosarcoma are occasionally considered for metastasectomies. A disease-free interval of >1 year from primary resection to recurrence was associated with improved outcomes after salvage surgery in our recent analysis at MDACC.

GASTROINTESTINAL STROMAL TUMORS

GISTs constitute the majority of mesenchymal tumors involving the gastrointestinal tract, with an estimated 2,500 to 6,000 cases per year in the United States. Although the clinical presentation of these tumors varies depending on tumor size and anatomical location, most tumors are found incidentally at the time of endoscopy or radiologic imaging. GISTs arise most frequently in the stomach (60% to 70%), followed by the small intestine (20% to 25%), colon and rectum (5%), and esophagus (<5%). Most GISTs are sporadic and, in 95% of cases, solitary. Most patients with GISTs present in the fifth to seventh decades of life, and these tumors are equally distributed between the genders. Symptoms of these lesions include pain and gastrointestinal bleeding, with abdominal mass a frequent finding.

Since the late 1990s, GISTs have been recognized as having distinctive immunohistochemical and genetic features. GISTs originate from the intestinal pacemaker cells (the interstitial cells of Cajal), which express CD117, a transmembrane tyrosine kinase receptor that is the product of the c-KIT proto-oncogene. Expression of CD117, found in at least 95% of cases, has emerged as an important defining feature of GISTs. The pathogenesis of these tumors is related to mutations in the c-KIT gene. Exploitation of this genetic characteristic has led to significant inroads into the development of successful therapy for these tumors.

Treatment

GISTs are an example of the power of targeted therapy in cancer therapeutics. In the past, surgical resection was the only treatment for GISTs. Although surgery remains the standard treatment for resectable tumors, the addition of systemic therapy has markedly improved outcome. The goal of surgery should be resection with a 1- to 2-cm margin if possible. For tumors located in the stomach, a wedge resection can often accomplish this goal. Minimally invasive techniques are commonly used in the management of GISTs. In cases with large tumors, preoperative therapy with a tyrosine kinase inhibitor (TKI) should be considered to decrease tumor size, which may downsize enough to change the extent of surgical resection. However, despite complete resection, recurrence is common in high-risk tumors. Factors such as large tumor size (>5 cm), tumor location in the duodenum or rectum, high mitotic count of >5 mitoses/50 high-power fields, and mutation status (such as deletion in KIT exon 9) are associated with increased risk of recurrence. In contrast, small GISTs (≤2 cm) with a low mitotic rate of ≤5 mitoses/50 high-power fields, located in the stomach are associated with low risk of further tumor progression and can be observed with serial endoscopic surveillance (6- to 12-month intervals) (NCCN Guidelines Version 2.2014).

The development of imatinib (Gleevec) has substantially increased the survival of patients with GISTs. Imatinib is a selective TKI of c-KIT and platelet-derived growth factor receptor alpha (PDGFR-α). Imatinib was approved in 2002 by the U.S. Food and Drug Administration after successful completion of trials that enrolled patients with metastatic and locally advanced disease (Table 5.3). Overall response rates were 48% to 71%, and median OS in patients with advanced GISTs who were treated with imatinib was 57 months compared with 9 months in historical

controls. The genotype of the c-KIT mutation is important: patients with mutations in exon 11 had higher response rates than did those with exon 9 mutations, although both groups responded better than did those without a mutation (wild type).

The benefit of imatinib in the postoperative setting was shown in a randomized controlled trial (ACOSOG Z9001) that enrolled 713 patients with GIST and KIT mutations after complete surgical resection. Patients who received 1 year of daily 400-mg Gleevec had better relapse-free survival than a placebo group had (98% vs. 83%; $p < 0.001$). The optimal duration of postoperative therapy was investigated in another randomized trial of postoperative imatinib at 400 mg/day for 12 versus 36 months. The results showed superiority with use of long (36 months) postoperative imatinib therapy (5-year survival rate, 92% vs. 82%; $p = 0.02$).

Because of the success of postoperative imatinib therapy for resectable disease and a reported high response rate to imatinib in advanced disease, imatinib has been used increasingly in a preoperative setting as well. The RTOG 0132/ACRIN 6665 phase II trial, which enrolled 63 patients with KIT-positive GIST, reported that 7% of patients had an objective response to preoperative imatinib (6 to 8 weeks), and stable disease was achieved in 83%. Whereas this study reported on the safety of preoperative imatinib therapy, Tirumani et al. reported that maximal tumor response is usually seen after 3 to 9 months, at which point surgery should be performed. However, even in patients who harbor the KIT mutation, 5% can still show primary resistance to imatinib and 14% will develop resistance at a later time. Sunitinib, another TKI with multiple targets including KIT, PDGFR, and VEGFR with different binding characteristics than those of imatinib, can be considered as second-line therapy in cases that do not respond or develop resistance to imatinib.

TABLE 5.3 Summary of Clinical Trials of Imatinib Mesylate in Patients with Advanced Gastrointestinal Stromal Tumor

Study, Year	Phase	No. of Patients	Overall Response	CR	PR	2-Year Overall Survival	Progression-Free Survival
Van Oosterom et al., 2001	I	36	53%	0%	53%	—	—
Demetri et al., 2002	II	147	54%	0%	54%	—	—
Verwiej et al., 2003	II	27	71%	4%	67%	—	73% (1 year)
Rankin et al., 2004	III	746					
– 400 mg daily			48%	3%	45%	78%	50% (2 years)
– 800 mg daily			48%	3%	45%	73%	53% (2 years)
Verweij et al., 2004	III	946					
– 400 mg daily			50%	5%	45%	69%	44% (2 years)
– 800 mg daily			54%	6%	48%	74%	55% (2 years)

CR, complete response; PR, partial response.

OTHER SOFT-TISSUE SARCOMAS

Sarcoma of the Breast

Sarcomas of the breast are rare tumors, accounting for less than 1% of all breast malignancies and less than 5% of all soft-tissue sarcomas. Various histologic subtypes occur within the breast, including angiosarcoma, stromal sarcoma, fibrosarcoma, and undifferentiated/unclassified sarcomas. Cystosarcoma phyllodes is generally considered to be a separate entity from other soft-tissue sarcomas because these tumors are believed to originate from hormonally responsive stromal cells of the breast and the majority are benign.

As with sarcomas at other anatomic sites, the histopathologic grade and size of the tumor are important prognostic factors. Complete resection with negative margins is the primary therapy. Total mastectomy carries no additional benefit if complete excision can be achieved by segmental mastectomy. Because of low rates of regional lymphatic spread, axillary nodal evaluation is not routinely indicated. Preoperative chemotherapy or radiation therapy may be considered for patients with large, high-risk tumors.

Desmoid Tumors

Desmoid tumors do not metastasize and are considered low-grade sarcomas. Approximately half of these tumors arise in the extremities, with the remaining ones originating in the trunk, abdominal wall, or abdomen/retroperitoneum (including the mesentery). Abdominal wall desmoids are frequently associated with pregnancy and are believed to arise as the result of hormonal influences. Patients with Gardner syndrome have a higher risk of mesenteric/retroperitoneal desmoid tumors than the normal population does, as an extracolonic manifestation. Desmoids that are small, asymptomatic and in a favorable site (superficial), can be managed initially with observation. Surgical resection with wide local excision should be the primary therapy for desmoid tumors; however, local recurrence may occur in up to one-third of patients. Postoperative radiation therapy has been associated with reduced incidence of local recurrence when used in patients with R1 margins in whom achieving negative margins would produce excessive morbidity. For desmoids that are unresectable or if surgery would be unacceptably morbid, definitive radiation therapy can also control tumor growth for an extended time period and should be considered. Systemic therapy with sulindac or other nonsteroidal anti-inflammatory drugs including celecoxib, tamoxifen, or toremifene, as well as more aggressive therapies such as doxorubicin-based chemotherapy, imatinib, or sorafenib can be considered for disease progression or recurrence. Progressive or recurrent desmoid tumors can be treated with systemic therapy, resection plus radiation therapy or definitive radiation (if not previously irradiated). Routine follow-up with appropriate imaging every 3 to 6 months for 2 years and then annually is recommended to evaluate for recurrence.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a neoplasm arising in the dermis that may occur anywhere in the body. Approximately 40% arise on the trunk, with most of the remaining tumors distributed between the head and neck and extremities. The lesion presents as a nodular, cutaneous mass that shows slow and persistent growth. Satellite lesions may be found in patients with larger tumors. Wide local excision is recommended, ideally with 2-cm margins; recurrence rates can be as high as 50%. Radiation therapy is recommended for positive margins if further re-resection is not able to be performed. In genetic analysis, the COL1A1-PDGFB fusion gene/protein is often detected. This has clinical relevance in that some

patients with metastatic dermatofibrosarcoma protuberans have responded to imatinib, a TKI of PDGFR. If fibrosarcomatous change is observed on pathologic review, tumors should be considered as high-grade soft-tissue sarcomas and treated as such.

BONE SARCOMAS

Osteosarcoma and Ewing sarcoma are the two most common malignant conditions of bone. Osteosarcoma has a peak frequency during adolescent growth, whereas Ewing sarcoma occurs most frequently in the second decade of life.

Presentation

The most common presentation of bone sarcomas (Ewing sarcoma or osteosarcoma) is pain or swelling in a bone or joint. As with soft-tissue sarcomas in adults, often a traumatic event draws attention to the swelling and can delay the correct diagnosis. Osteosarcoma most commonly involves the metaphysis of long bones, especially the distal femur, proximal tibia, or humerus. Ewing sarcoma may involve flat bones or the diaphysis of tubular bones such as the femur, pelvis, tibia, and fibula. Ewing sarcoma may also occur in soft tissues. Chondrosarcoma occurs most commonly in the pelvis, proximal femur, and shoulder girdle.

Up to 25% of patients presenting with osteosarcoma or Ewing sarcoma have metastatic disease at presentation. The most frequent metastatic sites for osteosarcoma include the lung (>90%) and the bone (10%), whereas Ewing sarcoma metastases occur in the lung (50%), bone (25%), and bone marrow (25%).

Staging

As with soft-tissue sarcomas, histopathologic grade is a crucial component of the staging of bone sarcomas. The surgical staging system for musculoskeletal sarcoma is based on the system by Enneking, which includes prognostic variables of histopathologic grade (G), the location of the tumor (T), and the presence of metastasis (M). The three stages are stage I (low grade), stage II (high grade), and stage III (metastatic). Stages I and II are then designated A (e.g., stage IA) if the lesion is confined within well-delineated surgical compartments and B if the lesion has

extracompartmental invasion.

Diagnosis

The evaluation of patients with a suspected bone tumor should include a history and physical, plain radiographs, and MRI of the entire affected bone. Bone scanning and CT of the chest are also necessary. On plain radiographs, malignant bone tumors show irregular borders, and there is often evidence of bone destruction and a periosteal reaction. Soft-tissue extension is also frequently seen.

A core-needle biopsy is the diagnostic procedure of choice when osteosarcoma is suspected. A core-needle biopsy performed under radiographic guidance should yield diagnostic findings in almost all cases of osteosarcoma.

Treatment

Effective multimodality therapy for childhood musculoskeletal tumors is critical to improve survival.

Surgery

Whenever feasible, limb salvage is the standard surgical approach to bone sarcomas. Successful limb-sparing surgery consists of three phases: tumor resection, bone reconstruction, and soft-tissue coverage. Complete surgical extirpation of the primary tumor and any metastases is essential, particularly in osteosarcoma because it is relatively resistant to radiation therapy. It is also desirable to resect Ewing sarcoma. If surgical removal with a wide surgical margin can be achieved, the prognosis is favorable (12-year relapse-free survival rate of 60%). However, Ewing sarcoma most typically involves the pelvis with an extensive soft-tissue mass that invades the pelvic cavity, which makes radical surgery difficult. Surgical resection is usually the only treatment indicated for the management of chondrosarcomas because this type of tumor is unresponsive to existing systemic therapies.

Chemotherapy

Chemotherapy has revolutionized the treatment of most bone sarcomas and is considered standard care for osteosarcoma and Ewing sarcoma. The bleak 15% to 20% survival rate with surgery alone during the 1960s has

improved to 55% to 80% in more recent reports by the addition of chemotherapy to surgical resection. Preoperative chemotherapy is an attractive option because it can lead to the downstaging of tumors, which then enables the maximal application of limb-sparing surgery. In addition, tumor necrosis that occurs after preoperative chemotherapy has been shown to be the most important prognostic variable determining survival.

The optimal chemotherapy regimen for osteosarcoma has still not been established, but agents most commonly used include doxorubicin and cisplatin; a methotrexate-containing regimen is a reasonable alternative. Multiagent chemotherapy has also been shown to be effective in Ewing sarcoma. Standard multiagent regimens include doxorubicin plus cyclophosphamide and a combination of doxorubicin, vincristine, and cyclophosphamide with or without actinomycin D (VDCA or VDC).

Radiation Therapy

Because osteosarcomas are generally radiation-resistant, radiation therapy is predominantly used for the palliation of large, unresectable tumors. In contrast, radiation therapy is the primary mode of treatment for most localized Ewing sarcomas. Preoperative irradiation may also be considered to reduce tumor volume before surgical resection is attempted.

Management of Recurrent Disease

Bone tumors disseminate through the bloodstream and commonly metastasize to the lungs and bony skeleton. In the past, only 10% to 30% of patients presenting with detectable metastatic osteosarcoma achieved long-term survival. More recent studies have shown that combined modality approaches consisting of surgical resection of the primary tumor and metastatic deposits in conjunction with multiagent chemotherapy can improve 5-year disease-free survival rates up to 47%.

Ewing sarcoma may recur in the form of distant disease as long as 15 years after the initial diagnosis. In a retrospective analysis of 241 patients with Ewing sarcoma of the pelvis, the major factors that influenced prognosis were tumor volume, responsiveness to chemotherapy, and adequate surgical margins.

Patients with suspected tumor recurrence should undergo a complete evaluation to determine the extent of disease. The resection of pulmonary metastases is the mainstay of treatment for patients with osteosarcoma. Prognosis can generally be determined by the response to previous

therapy, duration of remission, and extent of metastases. Multimodality therapy, including chemotherapeutic agents not previously used, is the general recommendation for treatment.

Sacrococcygeal Chordoma

The notochord remnant is the site of origin of the rare sacrococcygeal chordoma tumor. Chordomas are locally aggressive tumors that have a high propensity to recur. Because symptoms can be vague, diagnosis can be delayed. Surgical resection should involve a multidisciplinary team that includes the surgical oncologist, neurosurgeon, and reconstructive plastic surgeon. A two-stage procedure is frequently used at MDACC. First, the blood supply to the tumor arising from the iliac vessels is controlled through an anterior approach. Several days later, the tumor is resected via a posterior approach. Radiation therapy should be considered because of the high rates of local recurrence.

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6 Cancer of the Head and Neck

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OVERVIEW

The head and neck is composed of many different anatomic sites with heterogeneous structures, functions, and cellular origins. Due to this diversity, cancers arising in each area often have distinct risk factors for carcinogenesis, different presenting signs and symptoms, and unique diagnostic considerations. A variety of treatment options and resultant outcomes are dependent upon the size and location of the tumor, histology and molecular profile, presence of regional (cervical) and distant metastatic disease, specifics of prior treatment, comorbid disease status, and expected functional outcomes. This chapter will focus on cancers of the upper aerodigestive tract (divided into subsites), salivary gland, parapharyngeal space (PPS), sinonasal cavity, and temporal bone. Other cancers including melanoma, nonmelanoma skin cancer, carcinoma of the thyroid and parathyroid glands, sarcomas, and lymphomas are discussed separately in this handbook.

EPIDEMIOLOGY AND RISK FACTORS

Cancers of the head and neck comprise 3% of all cancers in the United States, not including cancers of the skin and thyroid, and about 85% are squamous cell carcinomas (SCCs). Median age of diagnosis is in the early 60s. Men are disproportionately affected with an incidence ratio ranging from 2:1 to 4:1. Current global estimates project more than 500,000 new cases of head and neck cancer (HNC) annually with approximately 62,000 new cases and 13,000 deaths expected in the United States per year. Among aerodigestive sites, cancers of the oral cavity (OC), oropharynx (OP), and larynx are most common in the United States, though the latter is declining in incidence. Cancers of the nasopharynx (NP) are more common in Southeast Asia, while those of the OC are most common in the

Indian subcontinent.

Risk factors for HNC are largely dependent upon anatomic location and differential exposures, explaining in part the geographic variations of the disease. Tobacco smoking is the most important carcinogen in HNC. Cigarette smokers have an estimated 5- to 25-fold increased risk, and cigar and pipe smokers also have an increased risk independent of cigarette smoking. The relative risk increases with duration of exposure but gradually declines after smoking cessation with no apparent excess risk by 20 years compared to nonsmokers. Long-term exposure to secondhand smoke also appears to be associated with increased risk of HNC. Alcohol is also an independent risk factor for cancers of the OC, pharynx, and larynx with consumption of 3.5 or more drinks per day increasing the risk of these cancers by 2- or 3-fold. Chronic tobacco and alcohol use by the same patient substantially increases the risk. Betel quid chewing, a widespread practice in Southeast Asia and India, is associated with increased risk for OC carcinoma. Risk of cancer of the upper aerodigestive tract from smoking marijuana has not been established and is difficult to analyze given the high rates of concomitant tobacco and alcohol use.

Viral oncogenesis is a well-known mechanism of HNC development and has received a tremendous amount of attention in the last 2 decades. Human papilloma virus (HPV), particularly types 16 and 18, is now recognized as the causative agent for greater than 70% of oropharyngeal carcinomas in the United States. Epstein–Barr virus (EBV) is the causative agent for most nasopharyngeal cancers, particularly in Southeastern China. Various occupational and/or environmental exposures have also been implicated in the development of HNC including asbestos, pesticides, wood, leather, and cement dust, formaldehyde, and various petrochemical products. Overall, studies of many of these exposures are limited by accurate quantification and potential misclassification of exposures in addition to the possibility that hidden culprits in manufacturing processes may represent the actual causative factors. Though most important in thyroid cancers, prior irradiation is also a low but known risk factor for SCC, sarcomas, and salivary gland cancers. Lastly, immunodeficiency such as that secondary to human immunodeficiency virus (HIV) or solid organ transplantation are associated with development of HNC (particularly nonmelanoma skin cancers), as are patients with congenital or acquired diseases such as Fanconi anemia, Li–Fraumeni syndrome, and Plummer–Vinson syndrome.

INITIAL EVALUATION, DIAGNOSIS, AND WORKUP

The most important aspect of an HNC evaluation is an early diagnosis. Unfortunately, no population-level screening tests currently exist, though development of oral sampling tests analogous to the Papanicolaou smear used in cervical cancer represents a promising area of research. For patients already known to be at high risk for the disease, serial examination of high-risk areas such as the OC can be essential to identify early cancers or premalignant lesions. The initial evaluation of a patient with known or suspected cancer of the head and neck should involve comprehensive visual inspection and manual palpation (where possible) of the skin of the scalp, ears, face, and neck, and mucosal surfaces of the eyes, nose, mouth, and throat. Visualization of the pharynx and larynx is aided by transoral mirror examination or transnasal flexible endoscopy. Middle ear pathology may require otomicroscopy and intranasal pathology often requires rigid examination with specialized endoscopes. Palpation of the salivary glands, thyroid, and lateral neck to assess for masses and/or pathologic lymphadenopathy is essential. In cases when a palpable mass in the neck is the patient's reason for initial cancer evaluation, its location can help guide efforts to determine the location of the primary tumor. Lastly, cranial nerve function should be carefully examined as both cancers and their subsequent treatments may result in nerve dysfunction.

Diagnostic imaging plays a central role in the evaluation and staging of HNC such that lack of need for cross-sectional imaging is rare in the workup of noncutaneous HNCs. Plain x-rays play a limited role in the modern evaluation of HNC with the exception of Panorex dental imaging and chest films for screening evaluation of secondary thoracic malignancy or metastases. Computed tomography (CT) of the head and neck provides excellent delineation of bony anatomy and the addition of iodinated contrast can yield precise detail on the presence of metastatic lymphadenopathy and soft-tissue invasion. Chest CT is also an important part of the initial evaluation since many patients may have concurrent lung pathology in addition to the fact that the lung is the most common site of distant metastases for cancers of the upper aerodigestive tract. Magnetic resonance imaging (MRI) is increasingly being used given its excellent soft tissue detail including the ability to demonstrate perineural and dural invasion, particularly in the case of salivary gland, paranasal sinus, and nasopharyngeal malignancies. Ultrasound is particularly sensitive in detecting cervical lymphadenopathy and has become the primary method

for evaluation of thyroid and parathyroid pathology. Positron emission tomography (PET) scans play a crucial role in the evaluation of distant metastases, and may be used in the evaluation of unknown primary tumors or for initial posttreatment imaging to determine response to therapy.

Pathologic diagnosis of head and neck malignancy is made on the basis of histologic examination of primary tumor biopsies and/or cytopathologic examination of fine-needle aspiration (FNA) biopsy for regional lymphadenopathy. In many cases, in-office biopsy may be performed for lesions that are easily accessible. Alternatively, patients may require examination under anesthesia with biopsy in several scenarios: if the tumor is not easily accessible or there is concern for tumor bleeding; to determine the location of the primary tumor when unknown; to evaluate for synchronous malignant lesions of the upper aerodigestive tract; to further delineate the specific extent of tumor prior to treatment planning. The latter scenario may be particularly important prior to surgical planning in certain oropharyngeal and laryngeal cancers. With modern ultrasound and histopathology, the need for excisional biopsy of an undiagnosed neck mass should be rare and a last resort for establishing a diagnosis, as this may violate the principles of oncologic surgery, complicate further surgery, and necessitate more intense adjuvant therapy. Nevertheless, if a diagnosis cannot be made through location and/or biopsy of the primary tumor; if cytopathology with the aid of ultrasound or CT guidance cannot establish a diagnosis; or if tumor histology is needed in excess of that afforded by core biopsy, an excisional biopsy may be warranted. In some cases, surgical planning may be made based upon a patient's history, the tumor location, and/or specific imaging characteristics without having a preoperative pathologic diagnosis. With rare exception, a pathologic diagnosis should be considered a necessity prior to considering nonsurgical treatment through radiation and/or systemic therapy in HNCs. Benign tumors or lesions resulting from systemic inflammatory or infectious diseases may closely mimic malignant tumors of the upper aerodigestive tract such that pathologic diagnosis is critical, particularly when aspects of the history or examination are incongruous.

STAGING AND TREATMENT

Staging for HNC is based on the American Joint Committee on Cancer (AJCC) classification and is outlined in Table 6.1. The T stage defines the size and extent of the primary; the N stage defines the size, number, and

location of nodal spread; and the M stage refers to the presence or absence of distant metastasis. Taken together, these form an overall TNM AJCC stage ranging from stage I to stage IV.

TABLE 6.1 American Joint Committee on Cancer Staging System for Head and Neck Cancers (Excludes Nasopharynx and p16-positive Oropharynx)

Stage Grouping	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0; T1–T3, N1, M0
Stage IVA	T4a, N0 or N1, M0; T1-4a, N2, M0
Stage IVB	Any T, N3, M0; T4b, any N, M0
Stage IVC	Any T, any N, M1
Primary Tumor (T) Dependent on Anatomic Location	
Regional Lymph Nodes (N)[a]	
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node <3 cm
N2a	Metastasis to a single ipsilateral lymph node >3 cm but <6 cm
N2b	Metastasis to multiple ipsilateral lymph nodes, all <6 cm
N2c	Metastasis to bilateral or contralateral lymph nodes, all <6 cm
N3a	Metastasis in a lymph node >6 cm
N3b	Metastasis to any lymph node(s) with ENE(+)
Metastatic Disease	
M0	No evidence of distant metastasis
M1	Evidence of distant metastasis

[a]Any patient with *clinical* extra-nodal extension (ENE) is *c*N3b whereas *pathologic* ENE is either minor (<2 mm) or major (>2 mm) and increases *p*N stage by 1 step (i.e., N1 to N2 or N2 to N3).

The mainstays of HNC treatment are surgery, radiation, and systemic therapy. In most cases, early cancers may be treated through a single modality, whereas advanced cancers require multimodality therapy. In some sites such as the OC, surgery represents the primary treatment modality largely due to the long-term morbidity of high-dose mandibular irradiation and the relative decreased sensitivity of these OC tumors to primary radiation therapy. In other areas such as the NP, radiation is preferred over surgery, given its high-degree effectiveness and relative surgical inaccessibility. Treatment of cancers of the larynx is largely dependent upon the size and location of the primary tumor and pretreatment function (i.e., respiratory, voice, and swallowing). In addition

to these factors, extent of regional metastases, HPV status, and smoking history are also central to treatment decision-making for oropharyngeal cancers. Overall, because of the many anatomic and histologic nuances of these cancers in addition to the functional impact of treatment, management of both early and advanced HNCs must be undertaken in a multidisciplinary setting and tailored to the patient. Providers routinely involved in these patients include radiation and medical oncologists, neuroradiologists, surgical and cytologic pathologists, dentists, speech language pathologists, clinical dieticians, plastic and reconstructive surgeons, neurosurgeons, and thoracic surgeons.

Even though this text focuses on surgical oncology, a surgeon's understanding of head and neck radiation and medical oncology is indispensable when determining the role and extent of surgery in care of the HNC patient. Though surgical and nonsurgical treatment specifics will be discussed at length by anatomic site, there are a number of scenarios where nonsurgical therapy is preferred. When surgery is the preferred treatment modality, it is usually performed prior to administration of radiation and/or systemic therapy with few exceptions. For instance, certain diseases such as some sarcomas may be treated with preoperative chemotherapy and/or radiation, while systemic therapy may be given prior to determining whether a patient should have surgical or nonsurgical treatment of their laryngeal cancer. In any case, surgical management of primary tumors of the head and neck follows the principles of en bloc resection whenever possible. Clearing surgical margins without transection or spilling of tumor is considered a basic oncologic tenant with the exception of some endoscopic endonasal surgery where piecemeal resection has been shown to be oncologically equivalent. Specifics of resection are discussed in detail below. This chapter deals specifically with cancer of the head and neck, though many lesions in this area of the body may be benign. In these circumstances, recommendation for surgical excision must involve balancing the following considerations with the reasonable risks of the procedure: growth over time versus stability; risk of malignant transformation; challenge for surveillance or accurate sampling on biopsy; aggressive behavior with local destruction; cosmetically conspicuous; current or anticipated decrement in function (swallowing, breathing, nerve deficit); and patient concerns regarding surgery versus observation.

Radiation therapy is delivered through administration of ionizing

radiation derived from either photons (e.g., x-rays and gamma rays) or particles (e.g., electrons, protons, neutrons, etc.) and can also be divided into either external beam and internal. Photons are delivered by external beam and most commonly produced with a linear accelerator but can also be produced from a radioactive source (historically cobalt). Particles are also produced by a linear accelerator with the most common types being electron, often used in treatment of skin cancer since these particles do not penetrate deeply, and proton, which remains relatively uncommon but is increasing in use nationwide including for certain HNCs. Brachytherapy refers to local deposition of a radioactive substance that releases radiation through decay. The most common substance used in treatment of HNC is iridium-192. Regardless of the type of radiation, all techniques are designed to deliver tumoricidal doses of radiation with minimization of treatment to normal tissues. Overall, external-beam photon treatment, delivered most commonly now through intensity-modulated radiation therapy (IMRT), represents the most common method for treatment of cancers of the upper aerodigestive tract. As far as dosing is concerned, primary treatment for cancers of the head and neck is typically administered between 66 and 70 Gy to the areas of known cancer (the primary and any positive nodes) and a slightly lesser dose to areas that may have cancer (the so-called elective treatment). When delivered after surgery (i.e., “postoperative” or “adjuvant” radiation), the dose is most commonly 60 Gy. Treatments are commonly given 5 days per week for 6 to 7 weeks. Dosing and algorithms for the treatment of other types of cancer such as melanoma, lymphoma, or sarcoma are different.

Systemic treatment in HNC most commonly refers to chemotherapy (i.e., cytotoxic drugs like cisplatin, 5-fluorouracil, or docetaxel), though also includes targeted treatments like monoclonal antibodies to EGFR (cetuximab) and checkpoint inhibitors to PD-1 (pembrolizumab, nivolumab). Systemic treatment can be given prior to surgery or radiation (i.e., “neoadjuvant” or “induction” therapy) in an effort to reduce the chance of distant spread of disease; as a type of “chemoselection” for patients whose cancers are particularly responsive to treatment; to reduce the size of large tumors prior to surgery or radiation; or prior to planned radiation in an effort to improve toxicity compared to concurrent treatment. When given together with radiation, chemotherapy acts as a radiation sensitizer, thereby producing greater treatment efficacy but also greater treatment side effects. Concurrent treatment is commonly used as a

primary treatment for disease confined locoregionally as well as postoperatively in the setting of positive surgical margins or extracapsular extension in lymph node metastases. Cisplatin (either high dose or low dose) and cetuximab are the most commonly used systemic agents.

Nodal metastases to the neck may be treated effectively through surgery and/or radiation with decisions between them determined by tumor histology, location, and other specifics such as the number of positive nodes and the presence of extracapsular extension. Neck dissection refers to surgical removal of regional lymphatics and may be performed to remove known (macroscopic) sites of metastatic lymphadenopathy, or to provide prognostic information in the case of subclinical (i.e., microscopic) disease. Several variations of this procedure exist, all of which involve removing lymphatics from different anatomic levels of the neck (Fig. 6.1). *Radical neck dissection* (RND) refers to removal of lymphatics from levels I to V in addition to the sternocleidomastoid muscle (SCM), internal jugular vein (IJV), and spinal accessory nerve. Due to the morbidity of this procedure, it is rarely performed. A *modified radical neck dissection* (MRND) reduces the morbidity of this procedure by preservation of one or more of these structures. Nevertheless, MRND is also often unnecessary since contemporary surgery seeks to confine dissection to levels which are at most risk for metastatic disease based upon location of the primary tumor. These surgeries are collectively referred to as *selective neck dissections* (SNDs) and can be subdivided into *supraomohyoid* (levels I to III), *lateral* (levels II to IV), and *posterolateral* (levels II to V). Indications for a specific type of SND are discussed by primary tumor site below. In cases where there is no evidence of nodal metastasis (stage N0), a neck dissection is called an *elective neck dissection* (END) and may be performed when the risk of regional metastasis exceeds a certain threshold. This threshold is generally recognized as 20% and is largely determined by known rates of microscopic nodal metastasis associated with a primary tumor of particular size and location. Lastly, neck dissection may also be performed to remove persistent or recurrent cervical lymphadenopathy after nonsurgical treatment, with the specifics of these surgeries determined by the location of nodal disease, the extent of postradiation changes (i.e., fibrosis and/or inflammation), and need for or ability to receive additional radiation after surgery.

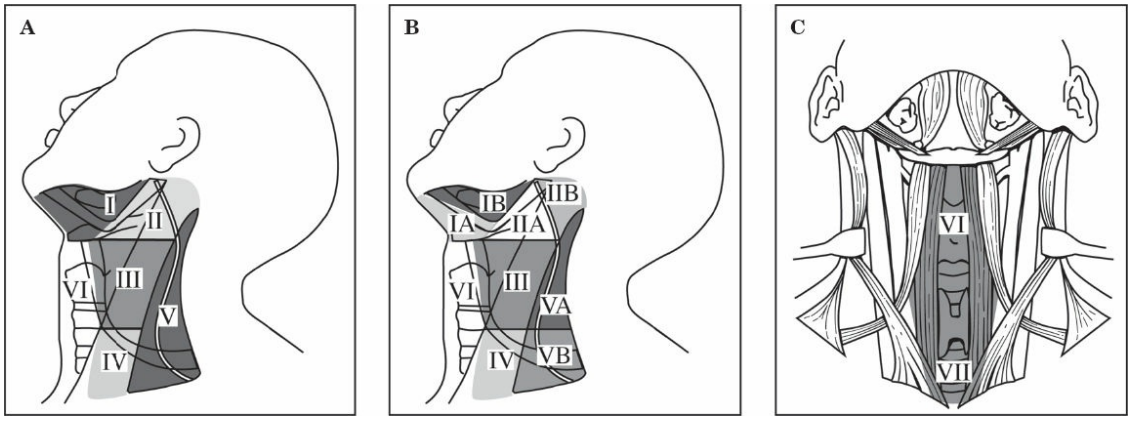

Figure 6.1 Anatomic lymph node levels. (Reprinted with permission from Fischer JE, Bland KI, Callery MP, et al., eds. *Mastery of Surgery, 5th ed*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

PROGNOSIS AND FUNCTIONAL OUTCOMES

As would be expected, prognosis for upper aerodigestive tract cancers is generally determined by the size of the primary, with bulkier disease being associated with a worse prognosis, in addition to the presence of regional and distant metastasis. Several other factors are also known to influence prognosis, typically through increased risk of regional and/or distant metastasis or local/regional recurrence. These include tumor grade, depth of tumor invasion, perineural and lymphovascular invasion by the primary tumor, close or positive margins, and the presence of extracapsular extension in lymph nodes. One advantage to surgical treatment is that pathologic determination of these factors is thus available (as opposed to that determined by clinical examination or imaging). Typically, presence of these factors often drives the decision for addition of adjuvant radiation or chemoradiation after surgery. Considering all sites and treatments, approximately 90% of patients achieve cure with stage I disease and roughly 70% with stage II. Survival continues to drop thereafter and the presence of nodal metastasis decreases survival by roughly 50%. This is largely associated with an increased risk of distant metastasis, which is estimated to occur in approximately 15% of all patients.

Similar to other disease sites within the body, ongoing efforts to identify biologic and molecular markers that are either prognostic or targetable through systemic interventions represent the new frontier of personalized oncologic treatment. Though the field of investigative tumor biology in head and neck SCC is broad, among the most well-recognized factors are

disruptive TP53 mutations, epidermal growth factor receptor (EGFR) and tumor growth factor-alpha (TGF-α) overexpression, and p16 expression (often used as a marker for HPV-associated oropharyngeal tumors). Tumor expression of programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein (CTLA-4) represents part of the evaluation of patients with recurrent or metastatic HNC during consideration of immunotherapy. Despite these advances, tailoring treatment on the basis of these molecular findings is often part of a clinical trial, particularly if that data are being used to reduce treatment intensity.

Apart from disease-specific outcomes, functional outcomes are also important considerations in the HNC population since both the tumor as well as treatment may have profound effects on normal function. Functional outcomes include both expected and unexpected sequelae of treatment and can also be divided into short- and long-term outcomes. In several areas of the head and neck, different types of treatment may achieve equal rates of cure, but one is often preferred based upon the anticipated functional outcome(s). For instance, in laryngeal cancer, a main goal of nonsurgical therapy is “organ preservation”, that is, treatment of the cancer without removal of the larynx. In this scenario, the patient has the potential to retain their ability to speak, eat, and breathe through their native upper aerodigestive tract. Conversely, advanced laryngeal cancer may have already damaged normal laryngeal function. For this reason, surgery would be the preferred treatment modality, since this function will only be worsened through radiation-based treatment. Understanding these types of outcomes requires prospective gathering of data on baseline and/or longitudinal function since these may change over time. Clinical trials provide an ideal setting for gathering prospective data, and determination of functional outcomes is no exception. In part due to fact that nonsurgical trials are historically much more common, comparatively robust data exist on the functional outcomes of patients treated with radiation with or without chemotherapy. Nevertheless, surgeons are becoming much more interested in prospectively tracking functional outcomes, particularly in treatment of cancers such as the OP and larynx where radiation is highly successful at treating the cancer but may have long-lasting side effects.

Similar to surgical risks and side effects, most radiation-associated side effects are predictable based upon the site(s) being treated. Indeed, many of the advances in radiation therapy delivery and technique have centered

on maintaining treatment of the cancer while minimizing radiation to normal structures such as the salivary glands, muscles of deglutition and mastication, and the laryngeal framework (for nonlaryngeal cancers). These have resulted in improvements in xerostomia, dysphagia, aspiration, and trismus, though these remain among the most common long-term side effects. Other potential long-term risks include osteoradionecrosis (ORN) of the mandible and dental caries, thyroid dysfunction, sensorineural hearing loss, accelerated carotid atherosclerosis, and delayed cranial neuropathy. Given all of these considerations, functional outcome measures including patient-reported outcomes and clinician-determined metrics are essentially a mandatory component of both surgical and nonsurgical clinical trials and are increasingly becoming a common part of routine clinical care rather than reserved for patients with overt dysfunction.

ANATOMIC SITES

As previously discussed, the head and neck is composed of several different anatomic sites. Treatment of cancers in each area requires careful consideration of tumor histology and etiology, disease stage, location of surrounding structures, and preservation of function. The following sections will discuss HNC by these sites (and subsites), including relevant anatomy, common risk factors and cancer types, treatment considerations and rationale, and anticipated outcomes of therapy.

Oral Cavity

The OC refers to the region extending from the vermillion border of the lips to the circumvallate papillae of the tongue and junction between the hard and soft palate. Subsites include the lips, buccal mucosa, alveolar ridge, floor of the mouth, oral tongue, retromolar trigone, and hard palate. OC cancer is one of the most common cancers in the world, with an annual incidence of over 300,000 and nearly 150,000 deaths. Tracking incidence and mortality of this disease at a population level can be challenging though since skin cancers of the lips and cancers of the OP are often grouped together with it. Nevertheless, it is more common in men than women (~3–4 to 1) and occurs most commonly in the 6th and 7th decades. The majority of cancers in the OC are SCC, though cancers of the minor salivary glands also occur including mucoepidermoid carcinoma, adenoid

cystic carcinoma, and adenocarcinoma.

Common risk factors for OC SCC include tobacco smoking and smokeless tobacco, alcohol, and betel quid chewing. HPV does not play a significant role in OC SCC carcinogenesis, although it is common for large tumors of the tonsil or base of tongue to extend secondarily to the OC. Although poor dental hygiene does appear to be an independent risk factor, chronic irritation from dentures or other oral appliances and use of mouthwash have not been supported as causative factors by further research. Lastly, some patients have premalignant lesions including leukoplakia and erythroplakia. These lesions should be biopsied on initial evaluation and followed, if negative for malignancy, since they may transform to an invasive cancer. The risk of development of an invasive cancer for leukoplakia is estimated at between 1% and 18%, while erythroplakia is associated with a higher risk. In addition to detailed visual and manual physical examination, CT with contrast and/or MRI with gadolinium are very helpful for determining local extension of disease and presence of metastatic lymphadenopathy. OC tumor staging is shown in Table 6.2.

Surgery remains the treatment modality of choice for OC cancers in part due to the relative accessibility of these areas in addition to the long-term morbidity of high-dose OC radiation. OC cancers are also believed to be slightly less sensitive to ionizing radiation. Invasive cancers are typically removed with a 10- to 15-mm margin of normal-appearing tissue. Small excisions can be performed transorally and may be closed primarily, allowed to heal by secondary intention, or closed using a skin graft. Larger defects may necessitate a mandibulotomy or transcervical approach in addition to more complex reconstruction through local tissue rearrangement, regional flap reconstruction, or free tissue transfer. Lesions with periosteal involvement, extension into tooth roots, or frank invasion of the maxilla and/or mandible require bony resection to achieve negative margins.

TABLE 6.2 Oral Cavity Tumor AJCC Staging

T1	Tumor ≤2 cm AND ≤5 mm DOI
T2	Tumor ≤2 cm AND DOI >5 mm and ≤10 mm; tumor >2 cm but ≤4 cm AND DOI ≤10 mm
T3	Tumor >4 cm OR any DOI >10 mm
T4a	Tumor invades adjacent structures (cortical bone, maxillary sinus, or skin)
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery.

DOI, depth of invasion (not tumor thickness).

The incidence of regional nodal metastasis correlates with the size, grade, and depth of invasion of the primary tumor. The primary nodal basins of the OC are levels I to III. Most data on the risk of occult metastases in clinically N0 patients derive from analysis of oral tongue carcinoma, where lesions with less than 2 to 4 mm depth of invasion have a low rate of regional metastasis. As such, lesions with greater than 4 mm depth of invasion typically are treated with wide local excision and simultaneous supraomohyoid neck dissection. Small lesions that are N0 with borderline thickness and/or those in the midline with the potential for bilateral lymph node metastasis may be amenable to sentinel lymph node biopsy. In experienced hands, this procedure identifies sentinel nodes with a false-negative rate of less than 3%, which is comparable to that seen in melanoma. In general, all patients with clinically evident or biopsy-proven nodal metastases from OC cancer should have a therapeutic neck dissection at the time of primary resection.

External-beam radiation or brachytherapy implants have been used extensively in the past for primary treatment of OC carcinoma. This is rarely performed contemporarily given high rates of radiation-associated toxicities, particularly mandibular ORN, as well as dismal rates of salvage in cases of radiation failure. Radiation therapy is commonly used in the adjuvant setting for patients at high risk of locoregional recurrence, including the pathologic risk factors described above (e.g., positive margins, perineural invasion, multiple metastatic lymph nodes, extranodal extension), as well as for patients with large primary tumors and/or need for extensive reconstruction, since margins may be more difficult to ascertain and monitoring for recurrence may be more challenging. Occasionally, if a patient is known preoperatively to have indications for radiation of the primary lesion but has no evidence of regional lymphadenopathy (N0), neck dissection may not be performed in favor of elective adjuvant nodal radiation. Use of concurrent chemotherapy is often

recommended for positive margins or extracapsular extension. Treatment of early lesions of the OC (T1/T2) carries an 80% to 90% 5-year survival rate while more advanced lesions (T3/T4) have a 5-year survival of 30% to 60%, with decrements largely related to the presence of regional metastases.

Lips

Cancer of the mucosa (wet portion) of the lips is overwhelmingly SCC, with 90% being located on the lower lip, and largely results from smoking or chronic sun exposure. Cancers of the upper lip are much more commonly basal cell carcinomas and are typically classified as skin cancers. Lip cancer most commonly presents early as a nonhealing erythematous lesion with larger lesions causing pain or bleeding.

Lip cancers are almost always treated with primary surgery with the possible exception of lesions of the oral commissure, which present a challenge in reconstruction and may be better addressed with radiation. Beyond removal of the cancer, two primary goals of surgical management of lip cancer involve maintenance of oral competence and minimization of microstomia. Depending on the extent of resection, various types of closure or reconstruction may be needed ranging from wedge excision to local advancement or rotational flaps, to free tissue transfer such as the radial forearm free flap. Cancers of the lip uncommonly metastasize to regional lymph nodes, though elective dissection is recommended for tumors larger than 4 cm (T3/T4); those with perineural spread along the mental nerve; those with bony involvement; and for recurrent tumors. Use of adjuvant radiation or chemoradiation may then be recommended depending on final pathology.

Buccal Mucosa

Cancer of the buccal mucosa accounts for 5% to 10% of all OC cancers in the United States but upward of 40% in India. Smoking and concurrent alcohol use, smokeless tobacco, and betel quid chewing are the major risk factors. Pre-existing leukoplakia is more common for buccal mucosa cancer and patients also present with a nonhealing ulcer, pain, or cervical adenopathy. Induration of the cheek skin or facial paralysis indicates local invasion of tumor into adjacent structures, while trismus may be secondary to inflammation of the masseter or pterygoids or from frank pterygoid

muscle invasion.

Early tumors (T1/T2) may be treated primarily with surgery or radiation, though the latter may result in high rates of xerostomia, trismus, and ORN. Surgery should consist of transoral excision at least down to the buccinator muscle, though this muscle is not considered an adequate anatomic barrier to spread into the buccal space and should be removed if invasion is suspected. Once the tumor extends to the buccal space, no anatomic barriers exist to contain its spread and tumor size is no longer predictive of prognosis. Small excisions may be reconstructed with split-thickness skin grafting, while larger defects necessitate regional or free tissue reconstruction to minimize trismus secondary to contracture as well as optimize wound healing in anticipation of need for adjuvant radiation. Transposition or ligation of the parotid duct may be required. Nodal metastasis is uncommon in early buccal cancers but patients with T3–T4, N0 tumors should have supraomohyoid neck dissection at the time of tumor resection. Moreover, given concerns for local recurrence, which has historically been higher in buccal cancers than many other sites, patients with T3/T4 disease and/or extension into the buccal space should have adjuvant locoregional radiation regardless of nodal staging.

Alveolar Ridge

Alveolar ridge cancer is overwhelmingly SCC arising from the gingival mucosa if you exclude odontogenic tumors of the maxilla and mandible. Common risk factors include tobacco, alcohol, and possibly ill-fitting dentures. Patients usually present with a nonhealing ulcer, pain, bleeding, or loose teeth. Numbness of the teeth, lips, or chin, indicating invasion of the alveolar nerves (particularly the inferior branch) and extension onto the adjacent buccal mucosa, floor of mouth, or hard palate are also important considerations in the initial evaluation and treatment planning.

Due to the underlying bone in all of these cancers, surgery is the preferred treatment regardless of whether bone invasion actually exists, since primary radiation may result in exposed bone and predispose the patient to development of ORN. For inferior alveolar ridge (mandibular) lesions, marginal mandibulectomy is sufficient for early tumors with primary closure of mucosa or placement of a split-thickness skin graft. This should be done with caution in edentulous patients given risks of subsequent fracture in an already atrophic mandible. Tumors with evidence of cortical bone invasion should be managed with segmental

mandibulectomy and ideally should be reconstructed with osseous free tissue transfer such as a fibular free flap. Patients with comorbidities precluding extensive reconstruction may be allowed to “swing” without bony reconstruction. Titanium plating of the mandible without bony reconstruction may be considered in isolated cases for lateral mandibular defects but never for anterior defects as these are very prone to plate extrusion or fracture over time. For superior alveolar ridge (maxillary) lesions, inferior or infrastructure maxillectomy is typically required. The goal of reconstruction in these cases is to re-establish separation of the oral and nasal cavities and can be accomplished through placement of a prosthetic obturator or through free tissue reconstruction. Patients with T2–T4, N0 disease should have END with frequent use of adjuvant radiation for poor prognostic indicators on pathologic analysis of the primary tumor and lymph nodes.

Floor of the Mouth

Cancer of the floor of mouth accounts for approximately 10% to 15% of all OC cancers with the vast majority representing SCC. Patients may present with a nonhealing ulceration, obstruction of the submandibular duct, numbness of the tongue, or even dysarthria secondary to deep infiltration of the tongue or involvement of the hypoglossal nerve(s).

Surgery is the treatment of choice, though primary radiation may be used with similar efficacy with limitations and treatment sequelae similar to other OC sites. Transoral resection of the floor of mouth often involves removal of the submandibular duct orifice. This may require transposition of the duct posteriorly in the mouth if possible, or simply ligation as the submandibular gland should be removed during the level I neck dissection. Removal of early lesions may be reconstructed with split-thickness skin graft or allowed to heal by secondary intention. Larger tumors may require composite resection including partial glossectomy, or marginal versus segmental mandibulectomy. These cases require complex reconstruction for optimization of speech and eating, in addition to closure of the OC to prevent leakage of saliva into the neck.

Regional metastases are fairly common and may be bilateral. Patients with T3–T4, N0 cancer should definitely have neck dissection(s) whereas those with T1–T2, N0 disease lesions may be observed, subjected to sentinel node biopsy, or receive END. The use of adjuvant radiation or chemoradiation is then dictated by the pathologic details from surgical

resection.

Oral Tongue

The oral tongue refers to the anterior two-thirds of the tongue in front of the circumvallate papilla. Cancer in this area is almost exclusively SCC with rare exception; represents the most common cancer of the OC; and most commonly occurs on the lateral surface of the tongue at the junction of the middle and posterior thirds. Tobacco use and alcohol are common risk factors, though an etiologic agent remains unidentified in a subset of patients younger than 40 that may be increasing in incidence. Oral tongue cancer often presents as a painless mass, though larger tumors may cause local pain or numbness, bleeding, dysarthria, oral phase dysphagia, and referred otalgia.

Primary radiation (external beam and/or brachytherapy) can be effective for early tongue cancers but cannot provide pathologic information on the primary tumor or regional lymphatics, may require temporary tracheotomy placement, and patients are subject to the long-term sequelae of high-dose OC irradiation described above. As such, primary surgery is the treatment of choice and partial glossectomy is adequate for early tumors. Cancer can spread easily into the intrinsic and extrinsic tongue musculature, meaning that margins must be careful assessed visually and by palpation during removal to ensure clear margins with the first specimen. Primary closure, healing by secondary intention, or split-thickness skin graft placement are appropriate for smaller defects. Larger defects should be reconstructed with regional or free tissue transfer as this results in improved speech and swallowing outcomes.

Occult regional metastases are common in oral tongue cancer and depth of invasion is the strongest predictor, such that all patients with tumors ≥4 mm should have END. Levels I to III should be dissected, though some also advocate inclusion of level IV for oral tongue cancers. Adjuvant radiation to both primary and regional lymphatics should be delivered for poor pathologic markers since locoregional recurrence is often unresectable and represents the most common cause of death.

Retromolar Trigone

The retromolar trigone refers to the mucosa posterior to the last molar overlying the ascending ramus of the mandible. Cancer of this region is

rare though it is a common location of extension of tumors from other areas of the OC or OP. Patients often present with local pain, burning, and otalgia. Since the mandible is only covered by mucosa and periosteum in this area, tumors are often advanced at presentation with bone destruction. Trismus may indicate pterygoid involvement and numbness of the teeth and chin/lip may indicate mandibular invasion or direct spread along the inferior alveolar nerve. Surgery is the preferred treatment for all lesions and often requires at least marginal mandibulectomy. Primary radiation may be considered for early lesions though trismus, bone exposure, and local recurrence are significant risks. Transoral exposure frequently is assisted by a lip-splitting incision with a cheek flap or visor flap. Elective management of the neck through supraomohyoid neck dissection or radiation is recommended for T2–T4, N0 patients. Split-thickness skin grafting may be sufficient for small lesions but regional or free flap transfer for fasciocutaneous, myocutaneous, or osseocutaneous reconstruction is often required. Adjuvant radiation is frequently recommended for cancers with bone invasion and those with nodal metastases.

Hard Palate

Cancers of the hard palate are also rare, comprised equally of SCC and minor salivary gland cancers in the United States. Patients often present with a painless ulceration, although pain, bleeding, and ill-fitting dentures may also be seen at presentation. The palatal periosteum is a strong barrier to spread, although tumors may spread into the maxilla causing nasal symptoms and facial swelling or spread anteriorly/laterally to the alveolar ridge causing dental pain and loose teeth. Perineural spread can occur along the palatine branches of the maxillary nerve through the greater palatine foramen, into the pterygopalantine fossa, and into the cavernous sinus, particularly with adenoid cystic carcinoma. These patients may present with multiple cranial neuropathies including facial numbness and diplopia.

Surgery is the treatment of choice for cancers of the hard palate. Though preservation of bone may be possible in small lesions with wide local excision and healing by secondary intention or split-thickness skin graft placement, bone removal with partial palatectomy is the most oncologically sound approach. Larger tumors will require infrastructure maxillectomy or more extensive maxillectomy that may be aided by lip

split with lateral rhinotomy or a facial degloving incision. Reseparation of the oral and nasal cavities may be accomplished by use of a prosthetic obturator or regional/free tissue reconstruction. END is controversial since occult nodal metastasis appears to be less common and patients often receive adjuvant radiation to the primary, thereby making elective nodal radiation a more common approach. Patients with extensive, unresectable perineural disease may be treated with primary radiation extending from the primary tumor following nerve branches to the skull base, though surgery may play a role for control of local disease and quality of life.

Nasopharynx

The NP refers to the region between the nasal cavity and OP, bounded anteriorly by the choanae, posteriorly by the posterior pharyngeal wall, superiorly by the body of the sphenoid, inferiorly by the soft palate, and laterally by the Eustachian tubes and superior pharyngeal constrictors. NP cancer is uncommon in most parts of the world with the exception of Southeastern China as well as areas of Southeast Asia and California that are home to Chinese immigrants. In these areas, the incidence is 10 to 20 times higher. It tends to affect patients at a younger age than many other cancers of the upper aerodigestive tract with a median age of approximately 50 years. SCC is by far the most common cancer but lymphomas, minor salivary gland cancers, melanomas, and sarcomas are also known to occur.

Carcinoma of the NP is traditionally classified according to histologic findings by the World Health Organization: Type 1, keratinizing SCC; type 2, nonkeratinizing SCC; and type 3, undifferentiated or poorly differentiated carcinoma (including “lymphoepithelioma”). Types 2 and 3, often combined together as nonkeratinizing types, are strongly associated with EBV. With regard to other risk factors, consumption of salted fish at an early age, which are high in nitrosamine compounds, also appears to play a role. Moreover, certain haplotypes and specific chromosomal alterations seem to be associated with increased risk and may explain why nasopharyngeal carcinoma is four times more common in first-degree relatives of patients with these tumors.

Carcinoma often arises in the lateral NP, particularly in the fossa of Rosenmüller, which is a recess posterior to the Eustachian tube orifice. Due to this location, patients may present with middle ear effusion, unilateral nasal obstruction, or bloody nasal secretions. As the tumor

grows, it may cause complete nasal obstruction, hyponasal speech, and frank epistaxis in addition to localized pain, headaches, and trismus. However, a painless neck mass or bilateral neck masses are the most common presentation since the NP has rich lymphatic drainage. It may also invade superiorly into the cavernous sinus or laterally into the PPS causing both upper and lower cranial nerve deficits. Diagnosis is often made through FNA of cervical lymphadenopathy or endoscopic biopsy of the NP. In endemic areas, levels of immunoglobulin A against certain EBV-specific antigens has even been used as a screening tool for detection of early asymptomatic tumors. AJCC staging of nasopharyngeal carcinoma is listed in Table 6.3.

Radiation therapy represents the mainstay of treatment for the primary tumor owing to the inherent radiosensitivity, its relative surgical inaccessibility, and its infiltrative nature. Radiation therapy alone is often reserved for T1N0 patients only. Chemotherapy is used in the treatment of all other stages, often delivered concurrently in the form of cisplatin and adjuvantly (after concurrent treatment) with cisplatin and 5-fluorouracil or neoadjuvantly with docetaxel, cisplatin, and 5-fluorouracil. Surgery, either through endoscopic or radical (“maxillary swing”) procedures, remains a treatment that is almost entirely reserved for locally recurrent disease. However, reirradiation either through external beam or through brachytherapy is still the most common method for treatment of local recurrence. Persistent versus recurrent regional lymphadenopathy is addressed with neck dissection.

Survival is directly related to AJCC staging with approximately 90% 5-year overall survival for stage I dropping to less than 60% for stage IV. EBV-associated disease is generally accepted as a positive prognostic indicator compared to the keratinizing subtype. Moreover, posttreatment levels of EBV DNA in plasma appear to be a strong prognosticator for persistent disease and overall survival. Given reasonably high survival combined with disease occurring in younger patients, functional outcomes (particularly long-term radiation sequelae) are well known for survivors of nasopharyngeal carcinoma. Though improvements in imaging techniques to better delineate tumor location combined with advances in radiotherapy delivery have diminished some long-term effects, many remain including trismus, xerostomia, osteoradionecrosis of the facial bones and skull base, dysphagia, temporal lobe necrosis, and radiation-induced cranial neuropathies. Otologic complications are also common including chronic

Eustachian tube dysfunction with serous effusions and sensorineural hearing loss, the latter of which may be exacerbated by concurrent treatment with cisplatin.

TABLE 6.3 Nasopharynx AJCC Staging

Stage Grouping	
Stage I	T1, N0, M0
Stage II	T0–1, N1, M0; T2, N0–1, M0
Stage III	T0–2, N2, M0; T3, N0–2, M0
Stage IVa	T4, any N, M0; Any T, N3, M0
Stage IVb	Any T, any N, M1
Primary Tumor (T)	
T0	No tumor identified, but EBV-positive cervical node involvement
T1	Tumor confined to the nasopharynx, or extends to oropharynx/nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension or invasion of pterygoid and/or prevertebral muscles
T3	Tumor invades bony structures of skull base, cervical vertebrae, or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, and/or soft-tissue involvement beyond lateral pterygoid
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis to retropharyngeal lymph nodes(regardless of laterality), or unilateral cervical lymph nodes, ≤6 cm, and above caudal border of cricoid
N2	Metastasis to bilateral cervical lymph nodes, ≤6 cm, and above caudal border of cricoid
N3	Metastasis in a lymph node >6 cm and/or below caudal border of cricoid (regardless of laterality)
Metastatic Disease	
M0	No evidence of distant metastasis
M1	Evidence of distant metastasis

EBV, Epstein–Barr virus.

Oropharynx

The OP is composed of the soft palate, palatine tonsils, the base of the tongue, and the posterior and lateral pharyngeal walls from the soft palate

to the pharyngoepiglottic fold. It is estimated that approximately 15,000 new cases of oropharyngeal cancer are diagnosed each year in the United States, which has been increasing steadily for almost 4 decades. The disease is more common in men than women with a ratio of 4:1. SCC is the most common type of cancer to arise in the OP but minor salivary gland tumors, lymphoma, and sarcoma can also occur.

SCC in the OP classically arises from chronic tobacco and alcohol use, though HPV-associated carcinogenesis has become the primary etiologic agent, such that at least 70% of oropharyngeal cancers are now HPV-positive in the United States. HPV is a sexually transmitted infection, and although most sexually active people have been exposed to the virus, it remains unknown why a relative small minority of the exposed population develops oropharyngeal malignancy, often many years following purported exposure. It appears that a long latency period exists and the risk for development of HPV-associated oropharyngeal cancer increases with the number of sexual partners, particularly related to oral sex. Compared to patients with non–HPV-associated disease, patients with HPV-associated oropharyngeal cancer on average are slightly younger and lack a history of heavy tobacco use.

TABLE **6.4a** p16-negative Oropharynx Tumor AJCC Staging

T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤4 cm
T3	Tumor >4 cm or extension to lingual surface of epiglottis
T4a	Tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery

Referred otalgia, dysphagia, bleeding, trismus, and halitosis are among the presenting signs and symptoms of oropharyngeal cancer patients, though by far the most common presentation is a painless neck mass. Indeed, cancers of the OP have a high likelihood for regional metastasis and have become increasingly common, such that physicians should have a high index of suspicion for this disease in an adult who presents with an asymptomatic neck mass. Small primary lesions and cystic regional

lymphadenopathy are characteristic of HPV-associated oropharyngeal carcinoma, such that office-based pharyngoscopy may not reveal a primary lesion and FNA of the cystic fluid may fail to reveal malignant cells. In this circumstance, FNA should be repeated, ideally with ultrasound guidance, to sample the cyst wall. If this fails, one may consider examination under anesthesia with directed biopsies and excisional lymph node biopsy to establish a diagnosis. Alternatively, if the diagnosis is made on biopsy of a lymph node but no primary is identified on clinic examination or routine imaging (CT, MRI), a PET scan may be obtained to look for asymmetric uptake indicating a primary tumor, or examination under anesthesia performed with tonsillectomy and biopsies of the glossopharyngeal sulcus and tongue base. Staging for OP cancer is listed in Table 6.4a.

Both surgery and radiation therapy have long been used in the primary treatment of oropharyngeal cancer, though radiation therapy with or without chemotherapy represents the most common approach for patients with all stages of cancer. Traditionally, surgery for oropharyngeal cancers consisted of transoral resection using self-retaining retractors and head-light assisted, line-of-sight surgery; transcervical approach with suprahyoid or lateral pharyngotomy; or transmandibular approaches. Needless to say, strictly transoral resections were limited to small, accessible primaries. With the development of transoral surgical techniques using the CO_2 laser or through robotic surgical assistance, surgery for oropharyngeal cancer is being given renewed consideration for the management of T1/T2 cancers. Because of the high risk of nodal metastases, neck dissection should uniformly be performed in patients undergoing surgical resection of the primary tumor. Primary lymphatic drainage is to level II followed by levels III and IV. Retropharyngeal drainage also occurs and is of particular concern for lesions involving the soft palate. Moreover, drainage can be bilateral for midline structures, particularly those of the base of the tongue. The decision for surgery must also take into account the burden of nodal disease since traditional risk factors of multiple nodes and extracapsular extension found on neck dissection may trigger the recommendation for adjuvant radiation or even chemoradiation. In this circumstance, the patient may require triple modality therapy, whereas fewer overall treatment modalities may have been adequate in the absence of surgery.

An ever growing body of evidence has shown that HPV-associated

oropharyngeal cancers respond favorably to any treatment with over 80% 3-year overall survival compared to less than 60% with non–HPV-associated tumors. This, combined with the fact that these patients are often younger and healthier, has given rise to ongoing discussions about de-escalation of treatment through modern surgical techniques, lower radiation doses, and less toxic systemic agents or altered timing of administration. In fact, a new overall staging system unique to HPV-associated oropharyngeal carcinoma is forthcoming that closely resembles that of nasopharyngeal carcinoma (Table 6.4b). Many treatment questions are currently under investigation through clinical trials that are planned, ongoing, or recently closed to accrual. Outside of a clinical trial, the current standard of care for treatment of early (T1 N0–1) to intermediate (T2N0–1 and some T3N0) cancers is single modality radiation therapy to 66 Gy and concurrent, cisplatin-based chemoradiation to 70 Gy for advanced disease (T1–2 N2+, T3 N+, and all T4). Some consideration has also been given to use of concurrent cetuximab, which may be a less toxic regimen. Induction chemotherapy using cisplatin and 5-fluorouracil or paclitaxel, ifosfamide, and cisplatin may also be considered for very bulky or low (level IV) nodal disease prior to definitive radiation or chemoradiation in an effort to improve regional and distant tumor control, though this approach has not been shown to improve local control or overall survival. Lastly, functional outcomes, particularly long-term swallowing, have become a primary focus of oropharyngeal cancer treatment and prospective tracking of patient-reported and physician-determined functional outcomes has become paramount to allow for valid comparisons of treatment modalities beyond disease survival.

TABLE **6.4b** p16-positive (HPV-associated) Oropharynx AJCC Staging

Clinical Stage Grouping	
Stage I	T0–2, N0–1, M0
Stage II	T0–2, N2, M0; T3, N0–2, M0
Stage III	T4, any N, M0; Any T, N3, M0
Stage IV	Any T, any N, M1
Pathologic Stage Grouping	
Stage I	T0–2, N0–1, M0
Stage II	T0–2, N2, M0; T3–4, N0–1, M0
Stage III	T3–4, N2, M0
Stage IV	Any T, Any N, M1
Primary Tumor (T)	
T0	No primary identified
T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤4 cm
T3	Tumor >4 cm or extension to lingual surface of epiglottis
T4	Tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
Regional Lymph Nodes (N), Clinical	
cN0	No regional lymph node metastasis
cN1	Metastasis to one or more lymph ipsilateral lymph nodes, all <6 cm
cN2	Metastasis to bilateral or contralateral lymph nodes, all <6 cm
cN3	Metastasis in a lymph node >6 cm (regardless of laterality)
Regional Lymph Nodes (N), Pathologic[a]	
pN0	No regional lymph node metastasis
pN1	Metastasis to ≤4 lymph nodes (regardless of laterality)
pN2	Metastasis to >4 lymph nodes (regardless of laterality)
Metastatic Disease	
M0	No evidence of distant metastasis
M1	Evidence of distant metastasis

[a]Note that pN3 does not exist.

TABLE 6.5

Hypopharynx Tumor Staging

T1	Tumor limited to one hypopharynx subsite, ≤2 cm
T2	Tumor invades more than one subsite of hypopharynx or adjacent site, or >2 cm but ≤4 cm, normal vocal cord mobility
T3	Tumor >4 cm or with vocal cord fixation or extension to esophagus
T4a	Tumor invades cricoid/thyroid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Hypopharynx

The hypopharynx (HP) is composed of the posterior pharyngeal wall (from the hyoid to esophageal inlet), the pyriform sinuses, and the postcricoid area. It's bounded laterally and posteriorly by the inferior constrictor and the most distal part of the middle constrictor. Upward of two-thirds of cancers in the United States are located in the pyriform sinus with another 20% arising from the posterior pharyngeal wall. Postcricoid tumors are quite rare. HP cancers are most closely linked to chronic tobacco and alcohol use with SCC being the predominant histologic type. Rarely, cancers of the minor salivary gland, neuroendocrine tumors, or lymphomas can also arise. Patients commonly present with dysphagia, sore throat, referred otalgia, dysphonia from vocal cord paralysis, and weight loss. Neck masses are also common owing to the rich, bilateral lymphatic drainage of the HP. On initial examination, patients should undergo fiberoptic examination of the pharynx and larynx to assess tumor location and extent in addition to evaluation of vocal cord mobility. Imaging is often obtained using CT scan with improved visualization of the HP through dynamic maneuvers such as Valsalva. Staging for HP cancer is shown in Table 6.5.

Cancers of the HP can be treated with either surgery or radiation as the primary modality. Numerous partial open pharyngectomy procedures can be found in head and neck surgical textbooks along with descriptions of transoral techniques. Overall, laryngeal-preserving surgery for management of HP cancer is not common since this requires lesions to be small and not involve the pyriform apex. Treatment of at least the unilateral nodal basin is mandatory either through neck dissection or postoperative radiation, though bilateral nodal treatment is typically necessary owning to the bilateral lymphatic drainage of the HP. As a result, most patients with early and advanced disease are treated nonsurgically with either radiation alone or concurrent chemoradiation with high-dose cisplatin. Unfortunately, trials examining both surgical and nonsurgical treatment often group sites of disease within the pharynx and larynx such that HP cancer represents a minority of cases. This makes extrapolation of findings more challenging. For the most advanced cancers (mostly T4) causing vocal cord paralysis, laryngeal cartilage destruction, and/or pretreatment evidence of aspiration, surgery consisting of total laryngectomy with partial or total pharyngectomy is the treatment of choice and is often followed by adjuvant radiation or chemoradiation. For

recurrent cancers after nonsurgical treatment, total laryngectomy is arguably the only option though partial laryngectomy procedures may be considered in highly select cases. Despite advances in treatment intensification, survival remains poor for patients with HP cancer due to the rarity of patients presenting at an early stage, the aggressiveness of the disease with propensity for locoregional recurrence and distant metastases, and the numerous comorbidities that patients often have. Considered as a group, 5-year survival is less than 50% with most patients dying from a second primary tumor, from recurrent disease, or from distant metastases.

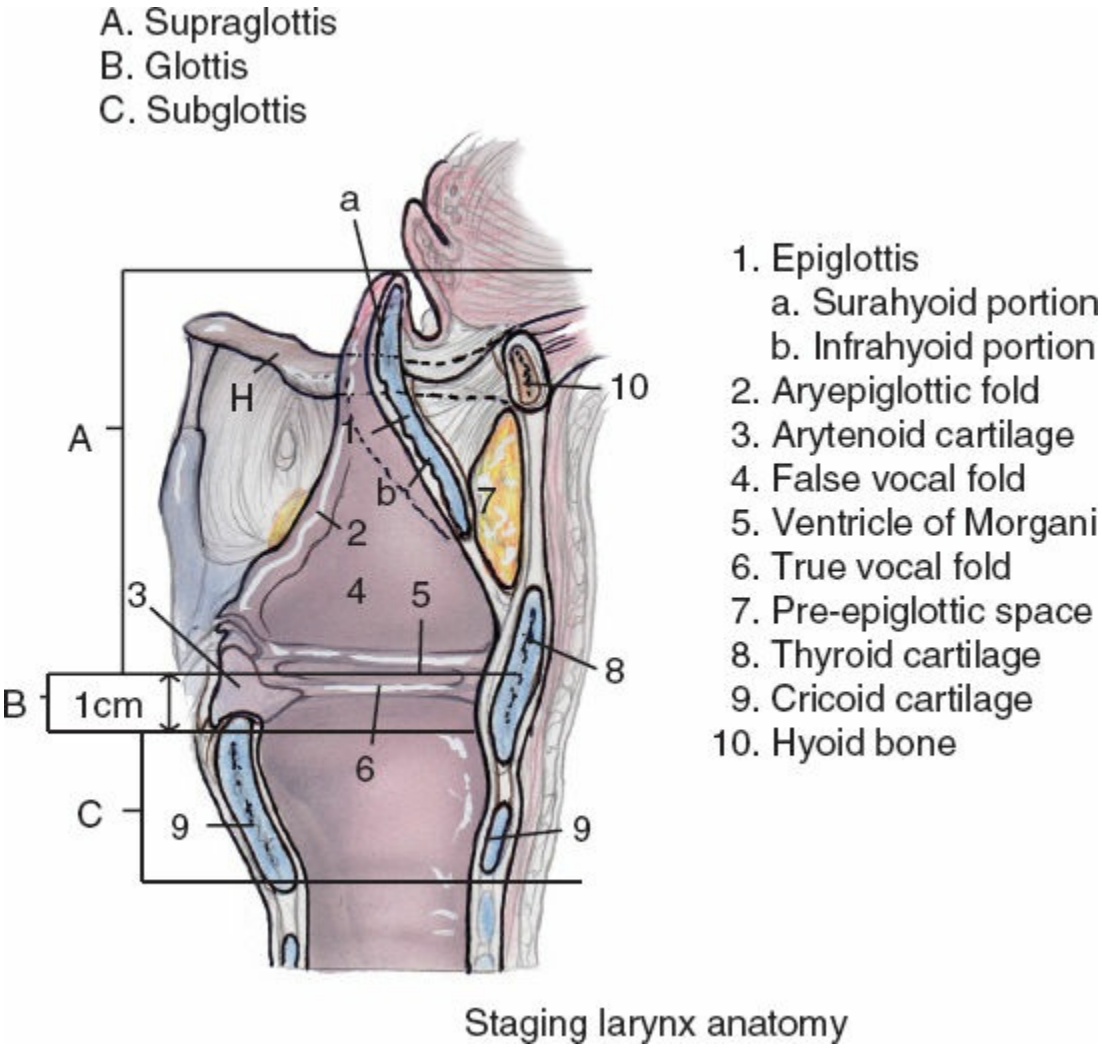

Figure 6.2 Laryngeal anatomy. (Reprinted with permission from Johnson J. *Bailey's Head and Neck Surgery, 5th ed*. Philadelphia, PA: Wolters Kluwer, 2013.)

Larynx

The larynx consists of three main subsites, the supraglottis, glottis, and

subglottis, each with its own distinct anatomic features and embryologic origins (Fig. 6.2). These in turn explain differences in the clinical behavior of cancers that can occur in each subsite. The supraglottis is composed of the epiglottis, aryepiglottic folds, arytenoid cartilage, false vocal cords, and the upper half of the laryngeal ventricle. The supraglottis has rich lymphatic drainage, which in part explains the more aggressive behavior of cancers in this area, particularly those arising in the "marginal zone" (the suprahyoid epiglottis and aryepiglottic folds). The glottis includes the lower half of the ventricle, the vocal cords including the anterior and posterior commissure, and the area extending 1 cm below the apex of the ventricle. The vocal cords (or folds) are comprised of several layers: epithelium, a gelatinous superficial layer, and more dense intermediate and deep layers (called the vocal ligament). The conus elasticus extends from the superior edge of the cricoid cartilage to the inferior surface of the vocal cord to merge with the vocal ligament. This structure is a strong barrier to lateral extension of cancer from the glottis and subglottis and also accounts for the relative paucity of lymphatic drainage in the area. Lastly, the subglottis extends from the inferior margin of the glottis to the inferior border of the cricoid.

SCC is the most common histology encountered in laryngeal cancer, though tumors can also originate from the minor salivary glands, cartilage, and neuroendocrine cells. Over 13,000 new cases are currently diagnosed annually in the United States, with approximately 60% starting in the glottis and 35% to 40% in the supraglottis. Tumors originating in the subglottis are very rare. Men are much more likely to develop both glottic and supraglottic cancer than women though the ratios are gradually declining. Overall, the incidence of laryngeal cancer is falling by 2% to 3% per year, in large part due to fewer smokers, which is the predominant risk factor and is dose-dependent. Alcohol has a synergistic effect with tobacco, particularly for cancers of the supraglottis. Certain occupational exposures are also known to be risk factors including wood and cement dust, asbestos, and certain fuels or industrial solvents. Secondhand smoke and HPV have much less commonly been implicated in laryngeal carcinogenesis.

The initial presentation of patients with laryngeal cancer depends in part on the anatomic location, though common symptoms include dysphagia or odynophagia, dysphonia, otalgia, weight loss, hemoptysis, and local pain. Patients with glottic cancer more often present with early-stage disease,

since lesions cause a change in voice, while patients with supraglottic cancer may be asymptomatic and present at a later stage. Evaluation of these patients should include laryngoscopy, ideally guided by a flexible or rigid laryngoscope, to precisely determine the location and size of the lesion in addition to the mobility of the vocal cords. Advanced lesions also require evaluation of swallowing function to determine the presence of clinical or subclinical aspiration prior to treatment. Patients require cross-sectional imaging of the neck and larynx for locoregional staging as well as imaging of the chest to assess for metastasis or secondary malignancies. Lastly, patients may require examination under anesthesia to establish a diagnosis or to assist with accurate delineation of tumor anatomy. In cases where airway compromise is impending or represents a significant risk, tracheotomy may be placed. Staging of laryngeal cancer is listed in Table 6.6.

As would be anticipated, either surgery or radiation can be reasonable primary treatment of laryngeal cancer depending on multiple factors including the location and stage of the cancer, its etiology and the presence of comorbidities, and the patient's pretreatment swallowing and respiratory status. Early cancers may be amenable to excision via transoral or open techniques or radiation alone. Endoscopic and partial open laryngectomies are technically challenging procedures that demand specific discussion outside the limits of this chapter. Lesions of the supraglottis may extend into the pre-epiglottic or paraglottic spaces and also have bilateral lymphatic drainage. For these reasons, surgical resection of early lesions must be carefully selected. Otherwise, radiation therapy is preferred. Early glottic lesions are approached similarly with regard to surgical resectability, though regional lymphatics are not a concern with smaller glottic tumors. Narrow-field radiation fields are used in these tumors, which spares some of the chronic sequelae of radiation. Treatment of T1a lesions may have better voice results with radiation alone, though it may prohibit use of radiation for future malignancy in high-risk patients. It is debatable whether lesions involving the anterior commissure have a higher propensity for recurrence given spread through Broyles ligament, though these are more challenging to resect and functional outcomes may be inferior to radiation.

TABLE

6.6

Supraglottis	
T1	Tumor limited to one supraglottic subsite
T2	Tumor involving more than one supraglottic subsite or adjacent glottic sites, normal vocal cord mobility
T3	Tumor limited to the larynx but with vocal cord fixation and/or invades the postcricoid area, paraglottic space, pre-epiglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumor extending through thyroid cartilage or invades tissues beyond the larynx (trachea, strap muscles, thyroid, esophagus, or oropharynx)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cord
T2	Tumor extension to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3	Tumor confined to larynx with vocal cord fixation, and/or invasion of the paraglottic space, and/or inner cortex of thyroid cartilage
T4a/b	Same as supraglottis
Subglottis	
T1	Tumor limited to subglottis
T2	Tumor extends to glottis, normal vocal cord function
T3	Tumor limited to larynx with vocal cord fixation Tumor invades cricoid/thyroid cartilage and/or invades tissues beyond the larynx (trachea, strap muscles, thyroid, esophagus, or oropharynx)
T4b	Same as supraglottis, glottis

Over the last several decades, treatment of advanced laryngeal cancer has undergone major changes, largely in the form of nonsurgical intensification aiming at laryngeal preservation without decrement in survival outcomes. Several large studies in the United States and Europe have demonstrated the feasibility of two nonsurgical approaches, namely induction chemotherapy followed by radiation, or concurrent chemoradiation. Specific results from these trials and the implications of their results can be found in the recommended readings. The goal of therapy for most patients with T1–T3 cancers is tumor eradication with preservation of laryngeal function. Total laryngectomy is often recommended for patients who have poor function, those with T4 cancers (usually from laryngeal cartilage destruction), and others who would not be able to tolerate nonsurgical treatment. Functional outcomes including

be able to tolerate nonsurgical treatment. Functional outcomes including speaking (or voice rehabilitation) and swallowing are a primary concern for laryngeal cancer survivors.

Salivary Glands

Tumors of the salivary glands can arise in any of the paired major salivary glands, the parotid, submandibular, or sublingual glands, or the minor salivary glands found throughout the mucosa of the upper aerodigestive tract. Cancer of the salivary glands is rare and is comprised of a heterogeneous group of malignancies with different biologic behavior. Upward of 70% of salivary gland tumors are found in the parotid gland, the majority of which are benign compared to the minor salivary glands, which are mostly malignant. Of note, the parotid gland is divided into two lobes, superficial and deep, by the course of the facial nerve. The superficial lobe contains lymph nodes that serve as the primary echelon of nodal drainage for anterolateral scalp, lateral face, and auricular cutaneous malignancies, meaning that a superficial parotidectomy should be included in surgical treatment of these malignancies when there is evidence of regional metastasis.

Parotid and submandibular tumors most commonly present as a painless mass. Pain, facial nerve weakness (parotid), weakness or numbness of the tongue (submandibular or sublingual), or hypomobility of the mass are indicators of possible malignancy. Tumors of the minor salivary glands often present with symptoms similar to SCC of the same areas though lesions are typically submucosal. Certain histologies may have a predilection for perineural spread such that numbness in the distribution of trigeminal nerve branches may be the only symptom. Risk factors include prior radiation exposure and smoking (for Warthin tumors) though most salivary gland neoplasms have no known environmental etiology. Lesions are typically evaluated with FNA for the major salivary glands or directed biopsy for the minor glands. FNA in this circumstance is most useful for providing a determination of the mass as salivary gland in origin, malignant versus benign, and possibly tumor grade (low vs. high). At times, a specific tumor type may be identified on cytopathology. Imaging may not be necessary for small, mobile lesions in the superficial parotid gland though both CT and MRI play an important role in clarification of the extent of all other lesions.

Among benign tumors, pleomorphic adenoma (also known as benign

monomorphic adenomas can also occur. Malignant tumors include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, salivary duct carcinoma, adenocarcinoma, SCC, lymphoma, and carcinoma ex pleomorphic adenoma, which arises from a pre-existing benign mixed tumor. In the case of a benign mixed tumor, there is approximately a 10% risk of malignant transformation over a 15-year period. Even though each of these malignant tumors have different defining characteristics with regard to propensity for locoregional recurrence or distant metastasis, surgery represents the mainstay of primary therapy in virtually all locoregional cases amenable to resection. Tumors of the superficial lobe of the parotid gland are addressed with superficial parotidectomy while total parotidectomy is reserved for lesions involving the deep lobe and/or those requiring facial nerve sacrifice. In general, all attempts are made to preserve the facial nerve in cases where it is functioning properly prior to surgery. For extensive tumors this may require identification of the facial nerve within the temporal bone through mastoidectomy. Similarly, submandibular gland tumors require excision of the entire gland at a minimum but extension of tumor into the surrounding tissues may require en bloc resection including surrounding soft tissue and potentially the hypoglossal, lingual, or marginal mandibular nerves if there is preoperative evidence of dysfunction or histologic involvement with tumor at the time of surgery. Surgery for tumors of the minor salivary gland tumors is also performed in en bloc fashion (with the possible exception of endoscopic endonasal resection).

Tumor grade is often important for treatment planning including need for neck dissection and use of adjuvant radiation therapy. Recommendations for END vary in the literature though it is generally performed for high-grade lesions, when there is evidence of major nerve invasion, or in the presence of intraparotid lymph node metastases. Radiation therapy is often recommended in an adjuvant setting for high-grade cancers as well as in those with advanced locoregional disease and with adverse features on pathologic review of the resected specimen. Moreover, radiation including proton and neutron therapy is sometimes used for control of disease in inoperable tumors though this broader application is based on results from small, published case series and is therefore challenging to interpret. Use of chemotherapy in salivary gland tumors is not common though high-grade tumors may respond favorably. Close follow-up surveillance is very important for higher-grade

Close follow-up surveillance is very important for higher-grade malignancies as they have a high rate of locoregional recurrence and distant metastasis.

Parapharyngeal Space

The PPS represents an anatomically complex potential space between investing layers of the deep cervical fascia where tumors can either arise primarily or spread from adjacent sites. Most often described as an inverted pyramid starting at the skull base and extending down to the greater cornu of the hyoid bone, the PPS is bounded medially by the constrictor muscles, laterally by the deep lobe of parotid and ramus of the mandible, posteriorly by the prevertebral musculature, and anteriorly by the pterygoid muscles. The carotid sheath is the most important group of structures located in this space, containing the carotid artery, internal jugular vein, and vagus nerve but cranial nerves XI and XII also exit the skull base through the jugular foramen and the cervical sympathetic chain runs just posterior to the carotid sheath.

Tumors arising in the PPS are uncommon and approximately 80% benign. Deep lobe parotid tumors extending into the PPS are the most common lesions (specifically pleomorphic adenomas) followed by paragangliomas, schwannomas, and neurofibromas. Numerous other tumors including sarcomas, meningiomas, and lymphomas can also rarely occur. Patients most often present with an asymptomatic neck mass causing blunting of the mandibular angle or inferior displacement of the submandibular gland. Alternatively, tumors may present with fullness of the soft palate or lateral pharyngeal wall and/or medial displacement of the palantine tonsil. This can mistakenly lead to the impression of tonsillar asymmetry and even a diagnosis of tonsil cancer. Lesions arising from nerves may present with corresponding deficits but the presence of pain, multiple cranial neuropathies, or trismus should raise clinical suspicion for a malignant process. Examination should include a complete cranial nerve assessment and palpation of the OP, parotid, and neck. Imaging prior to biopsy or other intervention is critical. Both CT and MRI are appropriate for evaluation of the PPS though MRI is often preferred for soft tissue detail. Diagnosis is often able to be made on radiographic appearance of the lesion and the pattern of displacement of neurovascular structures. At times, angiography may be beneficial to evaluate the blood supply of the tumor and even for embolization to minimize blood loss if surgery is

malignant tumor, as these lesions require more extensive treatment and counseling of patients is accordingly more important. Lastly, syndromes involving hereditary or multiple paragangliomas require special consideration as tumors of the head and neck may by bilateral, may be associated with tumors in other areas of the body, and may rarely possess catecholamine secretory function.

Treatment of tumors of the PPS depends largely on the type of lesion, the presence of functional deficits, the tumor's natural history, and the patient's overall health status. A period of observation of benign tumors is common to establish the rate of change, which is indolent for many PPS tumors. Benign tumors without significant and rapid growth may be monitored indefinitely, as sometimes the morbidity of surgery may exceed the potential benefit. When treatment is indicated, surgery is the mainstay of therapy for most lesions, with the goal being simultaneous tumor removal and preservation of neurovascular structures. Surgery is accomplished transorally in a minority of cases. More commonly, a transcervical or transparotid approach is used. For lesions requiring high exposure of the skull base, sometimes an anterior mandibulotomy is performed, although nasal intubation with anterior subluxation of the mandibular condyle is often sufficient to allow transcervical removal, especially for benign tumors. Suspected or known malignant tumors are treated with radical surgery and adjuvant radiation. Radiation has been advocated for local control of growth in patients who were unfit or declined surgical intervention. This approach is not widely performed since lesions often have a very slow growth rate and the long-term side effects of carotid sheath radiation are significant.

Nasal Cavity and Paranasal Sinuses

The nasal cavity extends in a dorsoventral dimension from the external nasal dorsum and pyriform aperture to the choanae and in a craniocaudal dimension from the nasal roof (frontal, ethmoid, and sphenoid bones or anterior skull base) to the nasal floor (maxilla and palatine bones). The nasal septum, which is composed of cartilage anteriorly and the vomer and perpendicular plate of the ethmoid bones posteriorly, divides the nasal cavity in half in the sagittal plane. There are four paired paranasal sinuses, maxillary, frontal, ethmoid, and sphenoid, each which communicate with the nasal cavity through their respective ostia. The nasolacrimal duct also drains into the nasal cavity. Lastly, three turbinates are found in each side

drains into the nasal cavity. Lastly, three turbinates are found in each side of the nasal cavity (inferior, middle, and superior) that serve to warm and humidify air during nasal respiration.

The nasal cavity and paranasal sinuses are lined by mucosa derived from ectoderm as opposed to endoderm like the rest of the upper aerodigestive tract. The mucosa is pseudostratified ciliated columnar epithelium containing mucinous and minor salivary glands, except at the nasal vestibule, which is lined by keratinizing squamous epithelium, and the superior septum/ethmoid roof, which is olfactory neuroepithelium. The sensory innervation to the nasal and paranasal mucosa is from branches of the trigeminal nerve (V1 and V2). The blood supply is from the external carotid (superior labial, angular, and internal maxillary arteries) and internal carotid (anterior and posterior ethmoidal arteries) arteries. Lymphatic drainage of the paranasal sinuses occurs via the retropharyngeal, parapharyngeal, and upper cervical lymph nodes. Staging for sinonasal malignancies is listed in Tables 6.7a and 6.7b.

TABLE **6.7a** Sinonasal Tumor Staging, Maxillary

T1	Tumor limited to sinus mucosa without bony invasion
T2	Tumor invades bone of hard palate or medial maxillary wall.
T3	Tumor invades bone of posterior maxillary wall or ethmoid sinuses, subcutaneous tissues, or floor/medial wall of orbit.
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid/frontal sinuses.
T4b	Tumor invades orbital apex, dura, brain, cranial nerves other than infraorbital (V2), nasopharynx, or clivus.

Benign tumors of the sinonasal cavity are reasonably common and include antrochoanal polyp, squamous papilloma, schneiderian papilloma, angiofibroma, osteoma, fibrous dysplasia, hemangioma, schwannoma, and benign minor salivary gland tumors. Nasal papillomas may result from HPV virus with squamous variants typically arising in the nasal vestibule. Schneiderian papillomas most often arise on the nasal septum or lateral nasal wall, can be locally destructive, and have a 5% to 15% risk of harboring carcinoma. Angiofibromas (also called juvenile nasopharyngeal angiofibromas) are benign, locally destructive, fibrovascular tumors

also have more common locations of origin, appearance on endoscopy, and imaging characteristics that aid in their diagnosis.

Sinonasal malignancies are rare, accounting for less than 5% of head and neck malignancies. The differential diagnosis for sinonasal malignancy is broad, including SCC, sinonasal undifferentiated carcinoma, small-cell neuroendocrine carcinoma, mucosal melanoma, several types of sarcoma, non–Hodgkin lymphoma, esthesioneuroblastoma (also called olfactory neuroblastoma), adenocarcinoma, and adenoid cystic carcinoma. SCC is the most common type, occurring predominantly in males in the 6th to 8th decades. Mucosal melanomas are rare (1% to 2% of all melanomas), with a fairly equal male-to-female ratio. Up to one-third may be amelanotic, and immunohistochemical analysis is important to establish the diagnosis. Risk factors for sinonasal malignancy are often thought to occur through occupational exposure. These include metal such as nickel, aluminum, and chromium for SCC, and wood and leather dust for adenocarcinoma. Smoking also plays an etiologic role in development of SCC and some evidence suggests outdoor air pollution is also correlated.

TABLE 6.7b Sinonasal Tumor Staging, Ethmoid

T1	Tumor limited to ethmoid with or without bony invasion
T2	Tumor extends into nasal cavity or adjacent paranasal sinuses with or without bony invasion.
T3	Tumor invades the floor/medial wall of orbit, maxillary sinus, palate, or cribriform plate.
T4a	Tumor invades anterior orbital contents, skin of nose or cheek, pterygoid plates, sphenoid/frontal sinuses.
T4b	Tumor invades orbital apex, dura, brain, cranial nerves other than infraorbital (V2), nasopharynx, or clivus.

The most common presenting symptoms for sinonasal tumors are unilateral nasal obstruction, facial pressure, pain, or numbness, rhinorrhea, anosmia, and epistaxis. Patients may also present with unilateral serous otitis media (due to obstruction of the Eustachian tube orifice), epiphora (due to obstruction of the nasolacrimal duct), or diplopia (from extension into the orbit or cavernous sinus). Nodal metastases are uncommon in sinonasal malignancies. Evaluation of the nose and paranasal sinuses includes external and endoscopic inspection. Unilateral masses are more

includes external and endoscopic inspection. Unilateral masses are more common to be neoplastic rather than inflammatory (i.e., polyps). Imaging (both CT scan and MRI scan) is important to determine the anatomic extent of the disease and can even provide the likely diagnosis in some cases. Imaging should often be obtained prior to biopsy since biopsy could potentially cause extensive bleeding or even cerebrospinal fluid leak.

As would be expected from such a broad group of tumors, treatment largely depends on the nature of the lesion. The development of endoscopic endonasal surgery has provided a natural orifice surgical option that appears to have similar oncologic outcomes and lower relative morbidity in the hands of high-volume surgeons in comparison to traditional transfacial and craniofacial resections. Surgery is the treatment of choice in almost all circumstances for benign lesions and most commonly is the primary treatment for malignancies as well. Exceptions to this include certain sarcomas treated with neoadjuvant radiation, lymphomas treated entirely by local radiation and chemotherapy, and certain biologically aggressive or initially unresectable lesions such as SCC, sinonasal undifferentiated carcinoma, small-cell neuroendocrine carcinoma, olfactory neuroblastoma, or salivary gland carcinoma that may be treated with neoadjuvant chemotherapy or chemoradiation. For advanced lesions invading the orbit, surrounding bony structures, or skin of the face, surgery may entail a partial or total rhinectomy, partial or total maxillectomy and adjacent sinuses (ethmoid and frontal), and orbital exenteration. Lesions involving the skull base with or without intracranial extension require collaboration with neurosurgery through endoscopic or craniofacial resection. Prognosis largely depends on the type and stage of the cancer, with most experts agreeing that survival is improved with multimodal therapy including surgery, radiation, and sometimes chemotherapy. Five-year overall survival approaches 60% for all types, is best for olfactory neuroblastoma (>70%), and worst for undifferentiated carcinoma (20% to 40%) and mucosal melanoma (10% to 30%).

Ear and Temporal Bone

The ear is composed of the external ear (pinna, auricle, and external canal), the middle ear, and the inner ear. The epithelium over the external ear is squamous with adjacent adnexal and glandular (sebaceous) structures while ciliated epithelium and glands line the middle ear. The framework of the auricle and outer third of the external canal is comprised

ear, the mastoid, and the inner ear are part of the temporal bone.

Although cutaneous malignancies of the pinna and auricle are common, cancers of the temporal bone are rare and account for less than 1% of all HNCs. The majority of tumors of the ear involve the auricle (>80%), followed by the ear canal, middle ear, and mastoid. Males are more commonly affected, and sun exposure is a major risk factor. SCC is the most common histologic cancer of the outer ear, followed by basal cell carcinomas. Paragangliomas, rhabdomyosarcomas, and adenocarcinomas can occur in the middle ear. More commonly, the temporal bone and ear are involved with cancer by extension from tumors or lymph node metastases of the parotid, temporomandibular joint, infratemporal fossa, or periauricular skin. Pain, aural fullness, conductive hearing loss, ulceration, and chronic otorrhea are common presenting symptoms. Deep extension may be associated with cranial neuropathies such as facial paralysis, vestibular symptoms, or sensorineural hearing loss. The most common tumor staging system for cancers of the temporal bone from the University of Pittsburgh is listed in Table 6.8.

TABLE 6.8 Temporal Bone Tumor Staging (University of Pittsburgh)

T1	Tumor limited to external auditory canal without bony erosion or evidence of soft-tissue extension.
T2	Tumor with limited external auditory canal bony erosion (not full thickness) or limited (<0.5 cm) soft-tissue involvement.
T3	Tumor eroding the osseous external auditory canal (full thickness) with limited (<0.5 cm) soft-tissue involvement, or tumor involving middle ear and/or mastoid, or patients presenting with facial paralysis.
T4a	Tumor eroding the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive (>0.5 cm) soft-tissue involvement.

Surgery is often the preferred therapy for SCC and basal cell carcinoma, although radiation therapy may play a role in highly selected cases. Small lesions of the outer ear are treated effectively by wide local excision, but partial or total auriculectomy may be required for larger lesions. Early external canal lesions can be effectively treated by sleeve resection. Lateral temporal bone resection is necessary for large tumors with medial extension or bony erosion, and subtotal temporal bone resections may be

extension or bony erosion, and subtotal temporal bone resections may be required for the most extensive tumors, though this treatment should be carefully considered in a multidisciplinary setting as prognosis remains poor. Extensive paragangliomas or sarcomas may be treated with primary radiation. Lesions arising elsewhere and invading the ear and/or temporal bone may require auriculectomy and/or lateral temporal bone resection. Adjuvant radiation therapy is commonly recommended. Survival for cancers of the outer ear is greater than 90% for cancers confined to the auricle, with worsening prognosis for those with medial extension into the ear canal, and middle ear extension with less than 30% long-term survival. Temporal bone malignancies have an overall survival rate of 20% to 30% at 5 years.

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7 Thoracic Malignancies

Scott Atay and Boris Sepesi

PRIMARY NEOPLASMS OF THE LUNG

In 2016, lung cancer accounted for an estimated 158,000 deaths and 224,000 new cases of cancer in the United States. With approximately 27% of all cancer deaths attributable to lung cancer, it is the most common cause of cancer-related death in both men and women, killing more people than the next three most common cancers combined (breast, prostate, and colon). Fortunately, as seen in Figure 7.1, the overall age-adjusted death rates for lung cancer have begun to decrease. This trend has been attributed to an overall decrease in the number of males who smoke and to no further increases in the number of women who smoke. Unfortunately, this good news is countered by a disturbing increase in smoking among certain minority and adolescent age groups. The overall 5-year survival rate for lung cancer is only 18%, primarily because the disease is usually advanced at presentation; if the disease is diagnosed and treated at an early stage, however, the 5-year survival rate approaches 60%.

Epidemiology

Smoking is the primary cause of more than 80% of lung cancers. The second most common cause of lung cancer is radon exposure. The third most common cause is secondhand smoke, which increases the risk of lung cancer by 30%. Despite the strong association between lung cancer and smoking, lung cancers develop in only 15% of heavy smokers. Giant bullous emphysema and airway obstructive disease can act synergistically with smoking to induce lung cancer, perhaps because of poor clearance and trapping of carcinogens. In addition, exposure to industrial and environmental carcinogens, including asbestos, uranium, cadmium, arsenic, and terpenes, has been implicated.

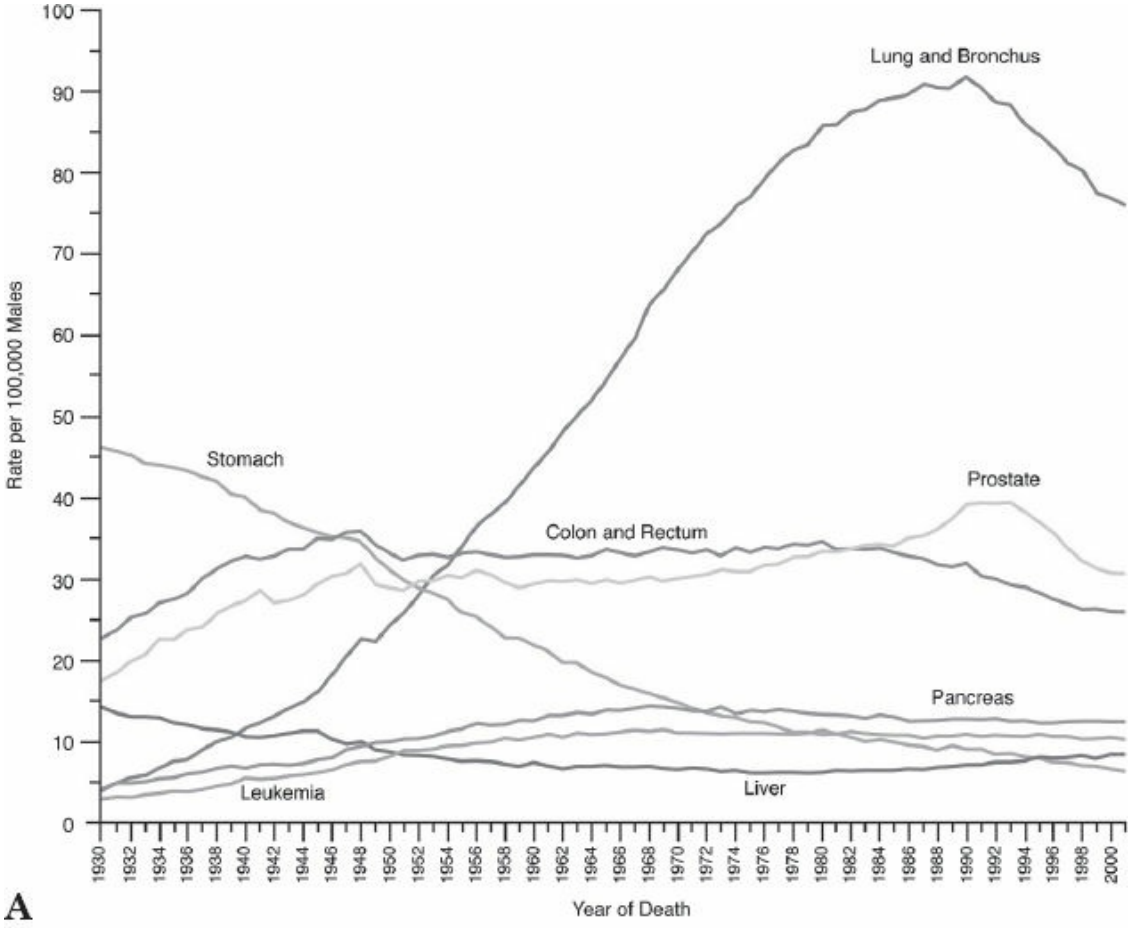
Pathology

Lung cancer can be broadly separated into two groups: non–small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). This is a popular division because, for the most part, NSCLC is often managed with surgery when the tumor is localized, whereas SCLC is almost always managed with chemotherapy with or without radiation therapy. The three major types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Table 7.1).

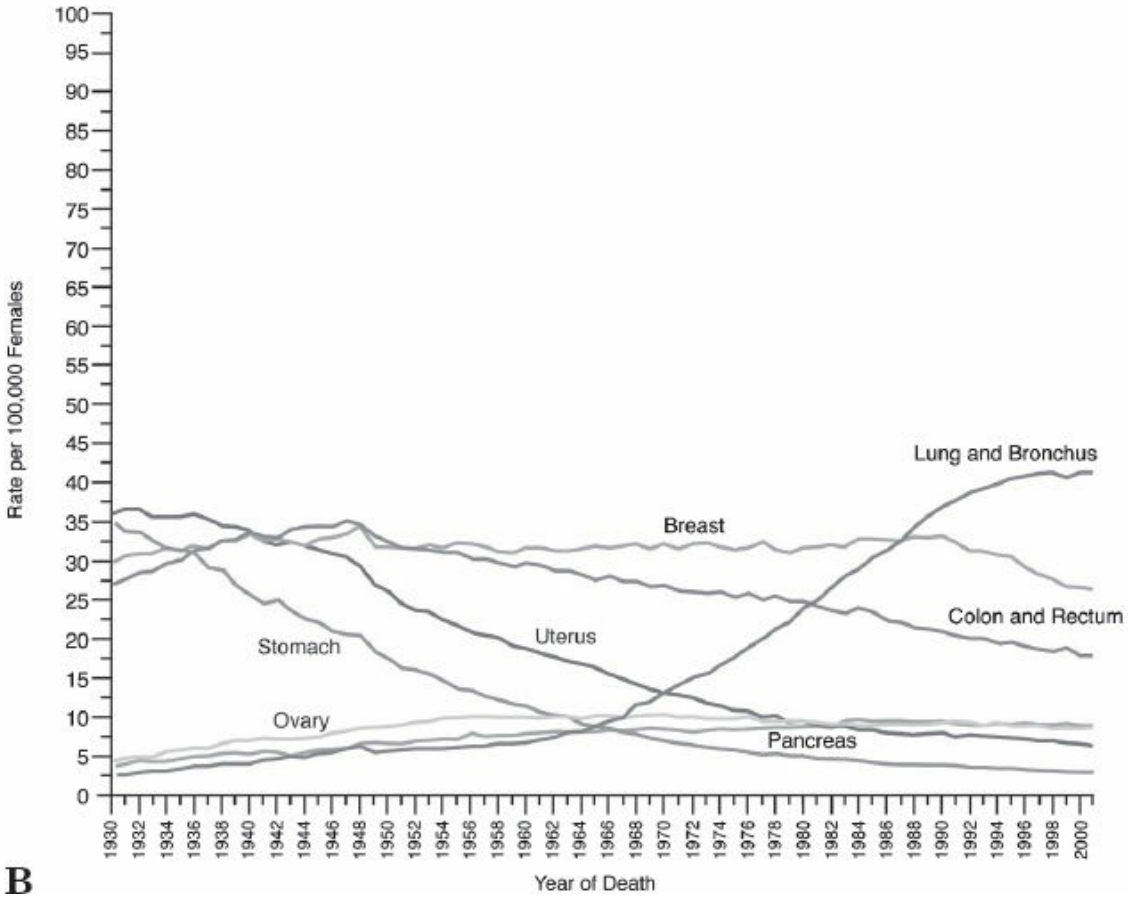
Non–Small Cell Lung Carcinoma

Adenocarcinoma is the most common type of NSCLC and accounts for more than 40% of cases. It is the most common lung cancer found in nonsmokers and women. The lesions tend to be located in the periphery of the lung and are more likely to develop systemic metastases, even in the face of small primary tumors.

Bronchoalveolar cell carcinoma/adenocarcinoma with lepidic growth is a subset of adenocarcinoma. The incidence of this tumor appears to be increasing. It occurs more frequently in women and nonsmokers and can present as a single mass, ground-glass opacity, multiple nodules, or an infiltrate. The clinical course can vary from indolent progression to rapid diffuse dissemination. This carcinoma, defined by tumor cells proliferating along the surface of intact alveolar walls without stromal or vascular invasion, is now referred to as adenocarcinoma with *lepidic* growth.


Rate per 100,000 Males
Lung and Bronchus
Stomach
Prostate
Colon and Rectum
Pancreas
Leukemia
Liver
Year of Death

A


Rate per 100,000 Females
Lung and Bronchus
Breast
Colon and Rectum
Uterus
Stomach
Ovary
Pancreas
Year of Death

B

Figure 7.1 Annual age-adjusted cancer death rates for selected cancer types in males (**A**) and females (**B**), United States, 1930 to 2001.

TABLE 7.1 Frequency of Histologic Subtypes of Primary Lung Cancer

Cell Type	Estimated Frequency (%)
Non–Small Cell Lung Cancer	
Adenocarcinoma	40
Bronchoalveolar	2
Squamous cell carcinoma	25
Large cell carcinoma	7
Small Cell Lung Cancer	
Small cell carcinoma	20
Neuroendocrine, well differentiated	1
Carcinoids	5

Squamous cell carcinoma accounts for approximately 25% of all lung cancers. Most (66%) present as central lesions, and cavitation is found in 7% to 10% of cases. Unlike adenocarcinoma, the tumor often remains localized, tending to spread within the pulmonary lobe or to regional lymph nodes rather than systemically; invasion of the chest wall, mediastinum, or other intrathoracic organs is also known to occur.

Large cell carcinoma accounts for approximately 7% to 10% of all lung cancers. Clinically, large cell carcinomas behave aggressively, with early metastases to the regional nodes in the mediastinum and distant sites such as the brain.

Small Cell Lung Carcinoma

Small cell carcinoma is associated with neuroendocrine carcinoma because of ultrastructural and immunohistochemical similarities. Small cell carcinomas are believed to represent a spectrum of disease beginning with the well-differentiated, benign/typical carcinoid tumor, moving to the intermediate less differentiated atypical carcinoids or neuroendocrine carcinomas, and ending with the undifferentiated malignant small cell carcinomas. Small cell carcinomas, which tend to grow fast and present with metastatic and regional spread, are usually treated with chemotherapy with or without radiation therapy. Even with seemingly low intrathoracic

disease volume, brain metastases may occur; therefore, prophylactic whole brain irradiation is indicated in all cases of small cell lung carcinoma.

Carcinoids tend to arise from major bronchi and as such are frequently central tumors that often present with cough or hemoptysis. Metastases are rare, and surgery is frequently curative. Immunohistochemically, carcinoids express neuron-specific enolase, chromogranin, and synaptophysin virtually without exception.

Neuroendocrine carcinomas or *atypical carcinoid*s occur more peripherally than typical carcinoids and have a more aggressive course, although surgery should still be considered according to clinical stage. Without appropriate immunostaining, they may be classified inadvertently as large cell carcinomas; Ki67 staining is used to estimate the aggressiveness of their behavior, and guide indications for systemic therapy.

Diagnosis

Signs and symptoms of lung carcinoma depend on the tumor size and location within the thorax. Some tumors may cause cough, hemoptysis, dyspnea, wheezing, and fever (often due to infection from proximal bronchial tumor obstruction). Regional spread of the tumor within the thorax can lead to pleural effusions or chest wall pain. Less common symptoms are superior vena cava syndrome, Pancoast syndrome (shoulder and arm pain, Horner syndrome [miosis, ptosis, anhidrosis], and weakness or atrophy of the hand muscles), and involvement of the recurrent laryngeal nerve, the phrenic nerve, the vagus nerve, or the esophagus. Paraneoplastic syndromes are found in 10% of patients with lung cancer, most commonly in those with SCLC. These syndromes are numerous and can affect endocrine, neurologic, skeletal, hematologic, and cutaneous systems. With the frequent use of computed tomography (CT), a number of tumors are discovered incidentally in otherwise asymptomatic patients.

A standard chest radiograph (CXR) is the initial diagnostic study for the evaluation of suspected lung carcinoma, followed routinely by CT. CT should include imaging of the liver and adrenal glands to rule out two common sites for intra-abdominal metastases. CT with intravenous contrast helps assess local extension to other thoracic structures and the presence of mediastinal adenopathy. At present, magnetic resonance imaging (MRI) adds little to the information gained by CT imaging, although it is indicated when evaluating superior sulcus tumors with

concern for neurovascular or spine involvement. Positron emission tomography (PET), especially integrated PET-CT, has become a frequent method of distinguishing benign from malignant pulmonary nodules. Although the accuracy of PET scanning in evaluating a pulmonary nodule can exceed 90% in some studies, clinicians should be aware that false-negative PET scans occur in patients with neoplasms having low metabolic activity (carcinoids and lepidic growth adenocarcinomas). Even with advances in imaging, histologic confirmation is always required to distinguish benign from malignant disease and to determine the histologic type of cancer. For a solitary lesion with a high index of suspicion (using Fleischner criteria based on size, growth, and risk category of the patient), histologic confirmation can be obtained at the time of surgery (thoracotomy or video-assisted thoracic surgery [VATS]) by using frozen sectioning of a wedge resection or a needle biopsy. If immediate surgery is not appropriate, then tissue from the tumor can be obtained by sputum cytology, bronchoscopy, or biopsy for central lesions; by electromagnetic bronchial navigation–guided biopsy or fine-needle aspiration (FNA) for more peripheral lesions; or by CT-guided core-needle biopsy or FNA. Patients with benign lesions should be monitored for interval growth with cross-sectional imaging performed every 6 months for at least 2 years to ensure stability.

Staging

The primary goal of pretreatment staging is to determine the extent of disease so that prognosis and treatment can be determined. In SCLC, most patients present with metastatic or advanced locoregional disease. A simple two-stage system classifies the SCLC as limited or extensive disease. Limited disease is confined to one hemithorax, ipsilateral or contralateral hilar or mediastinal nodes, and ipsilateral supraclavicular lymph nodes. Extensive disease has spread to the contralateral supraclavicular nodes or distant sites such as the contralateral lung, liver, brain, or bone marrow. Staging for SCLC requires a whole-body PET-CT scan and brain MRI.

The staging system for NSCLC—the International Lung Cancer Staging System or International Staging System (ISS)—was initially proposed in 1985. This system is based on tumor, node, and metastasis (TNM) classifications. Survival rates for patients with NSCLC by stage of disease are shown in Figure 7.2. Because of heterogeneity within groups, the

staging system has been continuously refined, with the most recent AJCC Cancer Staging Manual, eighth edition, staging classification being released in late 2016. This edition has further refinement of T-status, as well as additional subgroupings for metastatic disease which are beyond the scope of this chapter.

Staging of NSCLC involves a thorough medical history and physical examination, CXR, CT scanning of the chest and upper abdomen, and PET-CT scanning to look for occult metastases. Unfortunately, CT cannot definitively predict mediastinal nodal involvement because not all malignant lymph nodes are enlarged, and many enlarged nodes are simply larger because of previous infection. Lymph nodes larger than 1 cm on the short axis have a 30% chance of being benign, whereas lymph nodes smaller than 1 cm still have a 15% chance of containing tumor. PET-CT has a higher negative predictive value in the evaluation of mediastinal N2 disease (96%), although false positives can occur in patients with granulomatous disease, inflammatory processes, and rheumatoid nodules. Patients with subtle signs of possible distant metastases need to be examined more carefully, and PET scan represents an ideal test in this situation. A solitary site of possible metastasis by PET requires a biopsy of the site in question. Patients with discrete nodal enlargement on CT should undergo tissue confirmation of these nodes regardless of PET findings. Multiple medical societies recommend tissue confirmation of PET-positive mediastinal disease. Conversely, most investigators also agree that patients with early-stage (T1N0) lung cancer who have a PET-CT–negative mediastinum do not necessarily need invasive mediastinal staging to prove that the mediastinum is free of disease, since the addition of mediastinoscopy achieves only a <10% positive detection of N2 nodes in such a circumstance. With respect to the method of mediastinal sampling, both cervical mediastinoscopy and endobronchial ultrasound (EBUS) with biopsy are appropriate; lymphatic tissue harvest must be documented to ensure quality of nodal sampling. Brain MRI is indicated in larger or central tumors or clinical stage II disease. National Comprehensive Cancer Network guidelines can be consulted for further recommendations regarding staging and treatment algorithms.

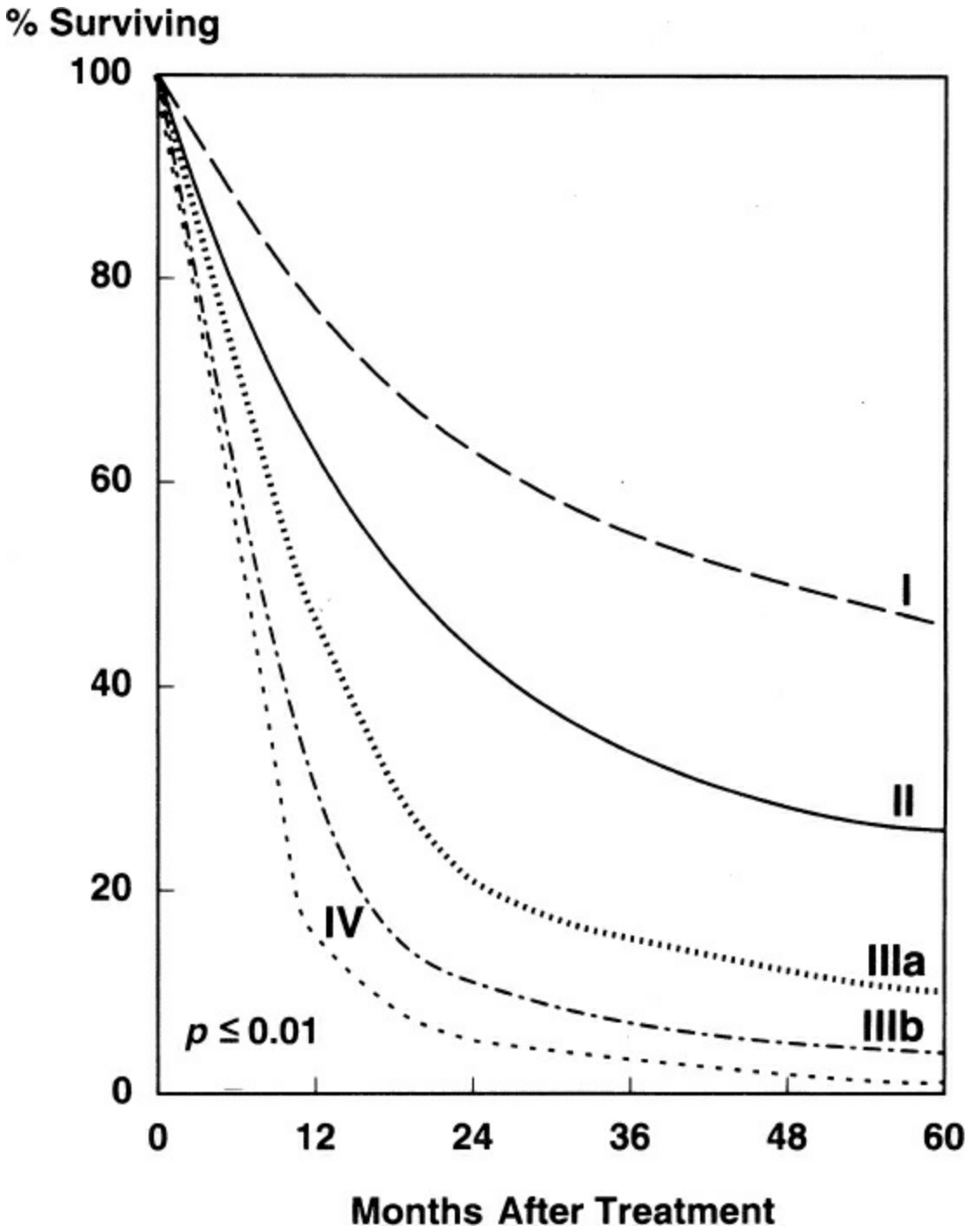


Figure 7.2 Cumulative survival according to clinical stage of non–small cell lung cancer.

Treatment

Pretreatment Assessment

Once a patient has been staged clinically with noninvasive tests, a physiologic assessment should be performed to determine the patient's ability to tolerate various therapeutic modalities. In addition to a general

evaluation of the patient's overall medical status, specific attention should be paid to the cardiovascular and respiratory systems. Cardiovascular screening should include a history and physical examination, as well as a CXR and electrocardiography. Patients with signs and symptoms of significant cardiac disease should undergo further noninvasive testing, including either exercise testing, echocardiography, or nuclear perfusion scans. Significant reversible cardiac problems should be addressed before therapy (i.e., chemotherapy, radiation therapy, or surgery) has begun.

The pulmonary reserve of patients with lung cancer is commonly diminished as a result of tobacco abuse. Simple spirometry is an excellent initial screening test to quantify a patient's pulmonary reserve and ability to tolerate surgical resection. A predicted postoperative forced expiratory volume in 1 second (FEV_1) of less than 40% of predicted or less than 0.8 L is associated with an increased risk of perioperative complications, respiratory insufficiency, and death. The predicted postoperative FEV_1 is estimated by subtracting the contribution of the lung to be resected from the preoperative FEV_1. In certain instances, the lung to be resected does not contribute much to the preoperative FEV_1 because of tumor, atelectasis, or pneumonitis. Thus, more accurate determination of predicted postoperative FEV_1 can be obtained by performing a ventilation–perfusion scan and subtracting the exact contribution of the lung to be resected. In good-performance patients with borderline spirometry criteria, oxygen consumption studies can be obtained that measure both respiratory and cardiac capacity. A maximum oxygen consumption (VO_2 max) of greater than 15 mL/min/kg indicates low risk, whereas a VO_2 max of less than 10 mL min^{-1} kg^{-1} is associated with high risk (a mortality rate of more than 30% in some series). Additional risk factors for lung resection include a predicted postoperative diffusing capacity or maximum voluntary ventilation of less than 40% and hypercarbia (>45 mm CO_2) or hypoxemia (<60 mm O_2) on preoperative arterial blood gases. For a summary of risk classification, refer to Table 7.2. In conjunction with clinical assessment (6-minute walk and number of flights of stairs climbed), these tests can help identify those patients at high risk of complications during and after surgical resection.

Preoperative training with an incentive spirometer, initiation of bronchodilators, weight reduction, good nutrition, and cessation of smoking for at least 2 weeks before surgery can help minimize

complications and improve performance on spirometry for patients with marginal pulmonary reserve.

TABLE 7.2 Pulmonary Assessment and Risk for Thoracic Resection

Average Risk	High Risk	Prohibitive Risk
ppoFEV1% > 40	ppoFEV1% 20–40	ppoFEV1% < 20
ppoDLCO% > 40	ppoDLCO% 20–40	ppoDLCO% < 20
pO_2 > 60	pO_2 45–60	pO_2 < 45
pCO_2 < 45	pCO_2 45–60	pCO_2 > 60
VO_2 max > 15	VO_2 max 10–15	VO_2 max < 10

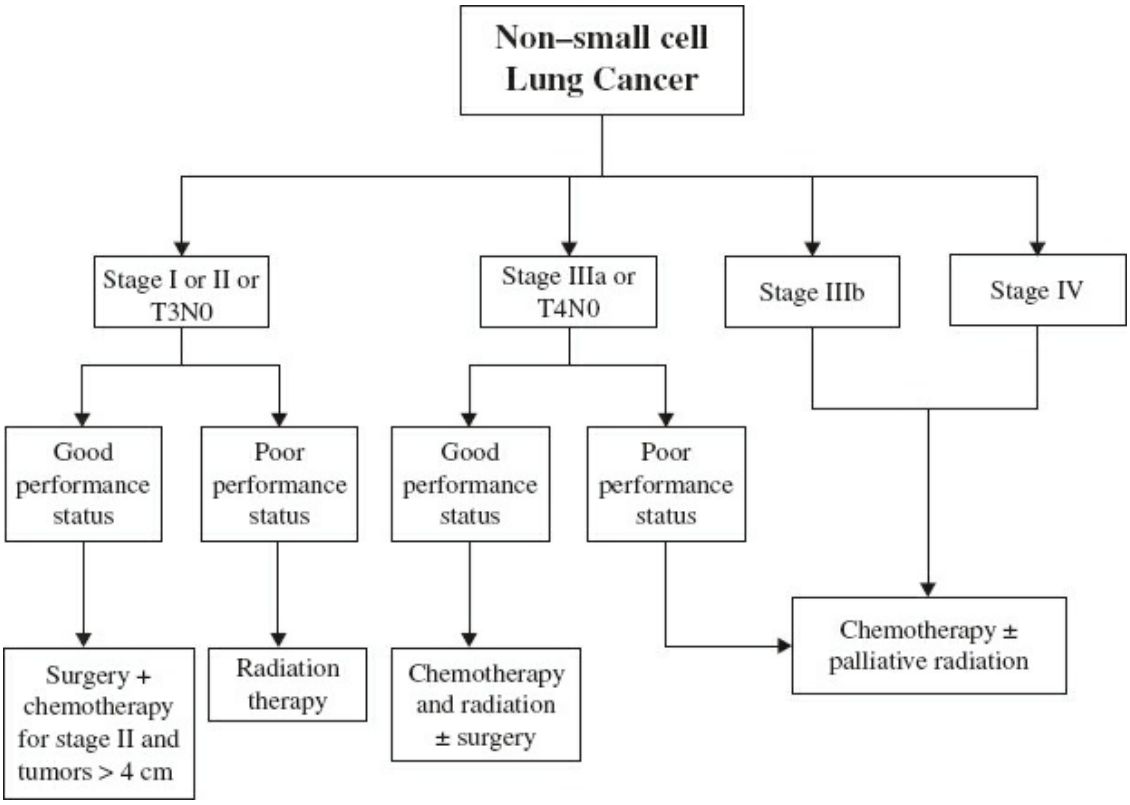


Figure 7.3 Algorithm for treatment of non–small cell lung cancer.

Treatment of Non–Small Cell Lung Carcinoma

In early-stage NSCLC, surgery is a critical part of treatment. Unfortunately, more than 50% to 70% of NSCLC patients present with advanced disease for which surgery alone is not an option. An algorithm for treatment based on clinical stage is presented in Figure 7.3. Physiologically fit patients with early-stage lesions (stage I or II) are

treated with surgery. A lesser resection (such as segmentectomy or wedge resection) or nonsurgical treatment (such as stereotactic radiation therapy) is indicated if lobectomy cannot be tolerated. Five-year survival rates of 60% to 70% and 39% to 43% can be achieved for patients with stage I and II disease, respectively. Chest wall involvement without nodal spread (T3N0) is considered an early-stage lesion (stage IIb). If these patients cannot tolerate surgery because of poor medical status, definitive radiation therapy combined with chemotherapy can result in survival rates of 15% to 35%.

The remainder of patients with stage IIIa disease (N2 disease or chest wall with nodal involvement) typically have a poor response to surgery alone, with 5-year survival rates of less than 15%. Induction therapy has been favored over postoperative adjuvant therapy for NSCLC with N2 nodal involvement based on earlier studies; however, recent retrospective series demonstrated similar outcomes with adjuvant chemotherapy for N2 disease. Preferably, induction therapy is recommended for all patients with single mediastinal nodal station biopsy–proven stage IIIa disease who are believed to be resection candidates. Patients who still require pneumonectomy after induction therapy may be better served with definitive chemoradiation because of the higher risk of mortality after pneumonectomy. The standard treatment for those with stage IIIb or IV disease includes chemotherapy (platinum-based doublets) and definitive radiation therapy for local disease control or palliation. Improved survival is obtained when chemotherapy is combined with radiation therapy, although the complication rate is increased.

Stage IIIb tumors are typically managed with definitive concomitant chemoradiation. They are generally not treated surgically since the contralateral mediastinal involvement portends aggressive disease biology. Surgical resection can be considered when the patient shows significant response to therapy and prolonged progression-free interval, although this is the rare exception. Metastatic disease is treated surgically only in the unusual circumstance of a solitary brain or adrenal metastasis with a node-negative lung primary. Several reports have documented better local control (in the brain and lung) with surgery in a subset of long-term survivors. The presence of mediastinal nodes, however, contraindicates surgical resection and mandates radiation therapy for the lung primary. In a recent randomized oligometastatic trial, improved progression-free survival rates were demonstrated after locoregional disease control with

either surgery or radiation therapy for up to three metastatic sites, compared with survival rates with chemotherapy alone. Patients were randomized after four cycles of chemotherapy to either more systemic treatment or locoregional and oligometastatic disease control with surgery or radiation therapy. The study was stopped prematurely because the primary study outcome was met before completion of the trial.

Surgery

Pneumonectomy

The removal of the whole lung was originally the most commonly performed operation for NSCLC; it now accounts for less than 20% of all resections. It is associated with higher mortality (4% to 10%) and morbidity than anatomical lobectomy. Advances in bronchoplastic and vascular reconstruction techniques have further obviated the need for pneumonectomy, even when faced with central tumors or those involving the lobar bronchi or pulmonary artery.

Lobectomy

Lobectomy is the “work horse” of lung cancer surgery. It is the most common procedure performed for lung cancer, with a perioperative mortality rate of approximately 2%, depending on the risk stratification. From an oncologic standpoint, lobectomy usually achieves complete tumor removal along with the resection of intralobar lymph nodes and the lymphatic pathway; it is the procedure against which all the other procedures and treatment modalities for local lung cancer are measured.

Lesser Resections

Segmentectomies and nonanatomical wedge resections may be associated with increased local recurrence when compared with lobectomy. The general consensus is that these procedures should be performed predominantly in higher-risk patients with limited pulmonary reserve and tumors <2 cm, who may not tolerate lobectomy. The advent of CT screening for lung cancer has led to increased identification of early-stage primary lung cancers in addition to their premalignant counterparts such as adenocarcinoma in situ or atypical adenomatous hyperplasia. The use of lesser resections for these early-stage lesions is currently being investigated in a phase III randomized controlled trial (CALGB 140543).

Minimally Invasive Thoracic Surgery

Minimally invasive thoracic surgery, although initially used only for early-stage tumors, has emerged as the preferred technique for many primary thoracic malignancies, with thoracotomy being reserved for more advanced disease or complex resections. A growing body of literature suggests that minimally invasive techniques are oncologically equivalent to open resection and may be associated with an improved perioperative morbidity profile. There are few absolute contraindications to a video-assisted approach, and although the degree of difficulty is increased with chest wall involvement, central tumors, significant hilar adenopathy, or calcified hilar lymph nodes, patients with these conditions can often be safely treated via a minimally invasive technique. Prior thoracotomy is not an absolute contraindication since the degree of adhesions and the ability to mobilize the lung adequately varies among patients. The degree of emphysema, comorbidities, and age are not contraindications, and patients so affected are not treated differently from patients undergoing standard thoracotomy. Recently, robotic-assisted techniques have gained a foothold in thoracic surgery. Although the clinical and oncologic outcomes are likely equivalent to those of VATS, the cost effectiveness of implementing robotic-assisted thoracic surgery still has not been established.

Extended Operations

Improvements in surgery and critical care have allowed certain tumors, previously considered unresectable, to be removed with acceptable morbidity and mortality. Carinal resections, sleeve resections, and extended resections for superior sulcus tumors with hemivertebrectomy and instrumentation of the spine can now be performed in a small subset of patients whose tumors were previously considered surgically unresectable. These procedures should be performed only in patients without mediastinal nodal involvement because 5-year survival rates are less than 5% for patients with extended resections in the presence of nodal involvement. Experienced multidisciplinary care is critical when addressing such advanced disease.

Mediastinal Lymph Node Dissection

Complete mediastinal lymph node dissection improves the accuracy of lung cancer staging, improves indications for subsequent adjuvant therapy, and may decrease locoregional recurrence, but improvement in overall

survival has not been conclusively demonstrated. In experienced hands, the morbidity rate associated with the addition of complete nodal dissection has not increased, compared with the rate associated with nodal sampling (removal of one or two nodes only from each accessible nodal station).

Radiofrequency Ablation and Targeted Radiation Therapy

Interest in nonsurgical local ablative therapies has increased in recent years in an effort to provide curative intent therapies to patients with early-stage lung cancer who are either unwilling or unfit to undergo operative pulmonary resection. With the advent of stereotactic body radiation therapy (SBRT) also known as stereotactic ablative body radiation (SABR) and encouraging short-term results in nonoperable patients, the use of SBRT as the first-line therapy for patients with resectable NSCLC and adequate pulmonary reserve has been gaining momentum amongst radiation oncologists. Two phase III randomized controlled trials (ROSEL and STARS) sought to answer the question of equivalency of SBRT to surgical resection; unfortunately, neither was able to accrue sufficient numbers of patients (only 3% of expected accrual). In a controversial publication, data from the two trials were pooled into an analysis of 58 patients, and authors concluded that SBRT is at least equivalent to lobectomy for early-stage NSCLC. In contrast, a review of the National Cancer Database suggested that SBRT was far inferior to surgical lobectomy with respect to overall survival at 5 years (29% vs. 59%). Given the lack of level I evidence and the uncertainty with respect to long-term outcomes, the role of SBRT/SABR for early-stage lung cancer is best reserved for patients with comorbidities precluding surgical resection.

Chemotherapy

Almost 50% of patients with NSCLC present with extrathoracic spread, and an additional 15% cannot undergo tumor resection because their locally advanced tumors are unresectable or because of the patients' inadequate pulmonary reserve. In addition, the long-term survival for patients who undergo complete resection of stage II or IIIa tumors remains below 50% and 30%, respectively. Therefore, the use of adjuvant chemotherapy to treat patients with unresectable tumors and to improve the results of patients with resectable tumors is an ongoing area of investigation. The Lung Adjuvant Cisplatin Evaluation (LACE) meta-

analysis demonstrated an additional 5% survival advantage with chemotherapy administered after surgery for stage II and III lung carcinoma. These data spawned numerous large adjuvant trials in Europe and America. The first positive study to be reported was the International Adjuvant Lung Cancer Trial, which enrolled nearly 1,900 patients with stage I, II, or IIIa disease who underwent complete resection. The group that received cisplatin-based doublet therapy had a 4.1% improvement in overall survival ($p < 0.03$), but a later analysis (7.5 years later) of the same population showed only statistically insignificant improvement in overall survival. Since the International Adjuvant Lung Cancer Trial, two additional positive trials (NCIC BR10 and CALGB 9633) have been conducted, which showed an 11% improvement in overall survival with the addition of chemotherapy after surgery compared with surgery alone at a median 9.3-year follow-up. The survival benefit was strongest in patients with stage II NSCLC. These studies generated a significant shift in the postoperative management of completely resected early-stage lung cancers. Evidence from these studies suggests that all patients with resected Ib (tumor larger than 4 cm) or higher-stage cancers should be evaluated by an oncologist for adjuvant chemotherapy and molecular profiling as appropriate.

Although studies using neoadjuvant chemotherapy for clinical stage Ib–IIIa disease have been not been as numerous, survival benefits of patients who received chemotherapy before surgery appear to be the same as those of patients who received chemotherapy after surgery. Several studies have examined the role of neoadjuvant chemotherapy for potentially resectable NSCLC. Collectively these studies demonstrated that (1) induction treatment had activity in NSCLC and elicited objective responses in at least 40% of the patients; (2) there was no significant increase in perioperative mortality; and (3) induction chemotherapy did not seem to negatively impact disease resectability. A meta-analysis of seven randomized trials demonstrated an overall survival benefit of 6% at 5 years. Given the similarity of these outcomes to the adjuvant data, the optimal timing of chemotherapy, adjuvant versus neoadjuvant, remains to be determined. Potential advantages to the neoadjuvant approach include improved tolerability, evaluation of sensitivity to treatment in vivo, and the ability to study biomarker modulation in response to therapy.

Molecular tumor profiling has become the standard of care, and patients with metastatic disease who manifest targetable epidermal growth factor

receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations receive the respective drugs erlotinib or crizotinib as first-line systemic therapy. Response rates to these drugs are far superior to those of standard chemotherapy, although platinum-based chemotherapy still has a role in the treatment of metastatic lung cancer. For a more complete list of biologic or genetic markers and their prognostic value, see Table 7.3.

Immunotherapy

Immune modulation as a potential therapeutic strategy for the treatment of advanced NSCLC was established with the FDA's approval (2015) of nivolumab, a human monoclonal antibody that targets the programmed death-1 (PD-1) cell surface membrane receptor. This checkpoint inhibitor disrupts the binding of PD-1 to its ligand (PD-L1) and allows the release of cytotoxic T cells to attack tumor cells. As a result, PD-L1 has become one of the most studied biomarkers to predict the response to immunotherapy. Studies evaluating the prognostic role of PD-L1 in NSCLC demonstrated that high PD-L1 expression correlated with diminished overall survival and poor tumor differentiation in immunotherapy-naive patients; however, high expression of PD-L1 was associated with a good response to immunotherapy suggesting value of PD-L1 as a predictive biomarker. Recently, pembrolizumab has been approved as the first line therapeutic agent in patients with metastatic lung carcinoma expressing PD-L1 > 50%. Prior to this study, the results of two phase III trials demonstrated an overall and progression-free survival benefit with the use of nivolumab compared with docetaxel for patients with metastatic NSCLC. Ipilimumab, an anti-CTLA4 immune checkpoint inhibitor, has also demonstrated activity in NSCLC, both as a single agent and when combined with nivolumab. Further investigation into the role of tumor-infiltrating lymphocytes, checkpoint inhibitors, and their costimulatory and coinhibitory molecules is ongoing and represents the next step in immunotherapy for lung carcinoma. Encouraging results in advanced disease have also led to the development of clinical trials to evaluate immunotherapy in neoadjuvant and adjuvant settings for patients with resectable NSCLC.

TABLE

Biologic or Genetic Markers and Their Prognostic Value

7.3 Value

Biologic Variable	Prognostic Factor	Reference
bcl-2	Favorable	Martin et al., 2003
TTF1	Adverse	Berghmans et al., 2006
Cox2	Adverse	Mascaux et al., 2006
EGFR overexpression	Adverse	Nakamura et al., 2006 Meert et al., 2002
Ras	Adverse	Mascaux et al., 2006 Hunckarek et al., 1999
Ki67	Adverse	Martin et al., 2004
HER2	Adverse	Meert et al., 2004 Nakamura et al., 2005
VEGF	Adverse	Delmotte et al., 2002
Microvascular density	Adverse	Meert et al., 2002
p53	Adverse	Steels et al., 2001 Mitsudomi et al., 2000 Huncharek et al., 2000
Aneuploidy	Adverse	Choma et al., 2001

Surveillance

Historically, the few treatment options for tumor recurrence in NSCLC have limited the cost-effectiveness of aggressive radiologic surveillance after surgical resection. This is changing, however, with the availability of novel treatments; accordingly, guidelines for surveillance will also need to be revisited. There is an increased incidence of second primary lung cancers (2% per year), and annual or semiannual cross-sectional imaging may help detect these lesions as well as possible recurrence. Any patient who experiences symptoms in the interim should also be evaluated aggressively for recurrence or a new primary. The lung, brain, bone, adrenals, and liver are the most common sites of metastases.

Small Cell Lung Carcinoma

Unlike NSCLC, SCLC tends to be disseminated at presentation and is therefore rarely amenable to cure with surgery or thoracic radiation therapy alone. Without treatment, the disease is rapidly fatal, with few patients surviving more than 6 months. Fortunately, SCLC is very sensitive to chemotherapy, and more than two-thirds of patients achieve a partial response after systemic therapy with multidrug regimens.

Treatment of SCLC therefore revolves around systemic chemotherapy. An algorithm based on the extent of disease is presented in Figure 7.4. Complete response is seen in as many as 20% to 50% of patients with limited disease, but these responses are not durable, and the 5-year survival rate is still less than 10%.

Chemotherapeutic regimens for SCLC most commonly include combinations of cyclophosphamide, cisplatin, etoposide, doxorubicin, and vincristine. Thoracic radiation therapy has been shown to improve local control of the primary tumor and is often included as part of the treatment for limited SCLC. In addition, because brain metastases are noted in 80% of patients with SCLC during the course of their disease, even patients who do not manifest brain metastasis should be treated with prophylactic cranial irradiation.

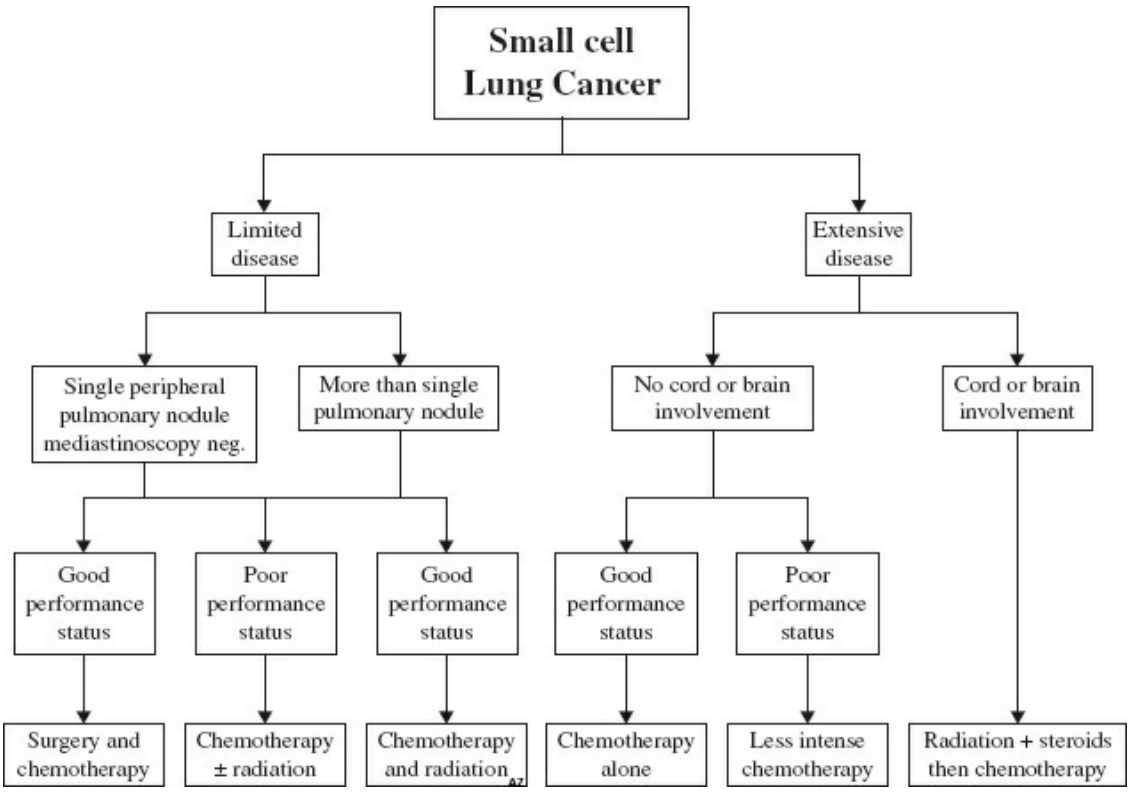


Figure 7.4 Algorithm for treatment of small cell lung cancer.

An infrequent but beneficial role for surgical resection of SCLC does exist. Solitary peripheral pulmonary nodules with no evidence of metastatic disease after evaluation with CT of the abdomen and chest, MRI of the brain, PET-CT, and mediastinoscopy can be treated with lobectomy, postoperative chemotherapy, and prophylactic brain irradiation. In these selected patients, a 5-year survival rate of 50% has been achieved for

peripheral T1N0 and T2N0. Surgery for more central lesions, however, has not been demonstrated to improve survival over that achieved with chemotherapy or radiation therapy alone.

METASTATIC NEOPLASMS TO THE LUNG

Pathology

The biology of the underlying primary malignancy determines the behavior of its metastases. Metastases may occur via any route, including direct extension to the chest.

Diagnosis

Because of their often peripheral localization, most pulmonary metastases remain asymptomatic, with fewer than 5% showing symptoms at presentation. Diagnosis is commonly made during radiographic follow-up after treatment of the primary malignancy. Planning of surgical interventions should be based on CT findings, even though CT scanning may still miss some small nodules found at surgery. As the resolution of CT scanning continues to improve, the number of missed nodules will likely decrease, whereas the number of subcentimeter, clinically insignificant nodules will rise.

When multiple new pulmonary nodules are present in patients with a known previous malignancy, the likelihood of metastatic disease approaches 100%. New solitary lesions, however, can represent new primary lung cancers because many of the risk factors are similar.

Staging

No valid staging system exists for pulmonary metastases. The International Registry of Lung Metastases has identified three parameters of prognostic significance: resectability, disease-free interval, and number of metastases. The criteria for offering patients resection of metastases include technical feasibility to achieve complete resection of all metastases, control of the primary tumor or plan to control the primary tumor, adequate predicted postoperative pulmonary reserve, and no extrathoracic metastases or plan to control those metastases with other local therapies. This final criterion should be viewed as a relative contraindication, since patients with liver and lungs metastases from colorectal primaries have achieved durable

results with complete resection. Patients who meet these criteria could be offered metastasectomy. Favorable histologies for long-term survival after resection include sarcoma and breast, colon, and genitourinary metastases. Unfavorable histologies include melanomas and esophageal, pancreatic, and gastric cancers. It should be noted that the landscape of systemic treatment options for various malignancies is changing so rapidly with the availability of novel chemotherapy, hormonal and targeted therapy, and immunotherapy that patient selection of pulmonary metastasectomy should be based on the latest knowledge and treatment options for that particular disease process.

Treatment

Surgery

Preoperative evaluation for resection of pulmonary metastases is similar to that of any other pulmonary resection. Because of the increased risk of recurrent metastases and the need for future thoracotomies, parenchyma-conserving procedures (wedge resection, laser, or cautery excision) are performed whenever possible. A variety of surgical approaches can be used.

Median sternotomy allows bilateral exploration with one incision. Lesions located near the posterior hilum can be difficult to reach, and exposure of the left lower lobe—especially in patients with obesity, cardiomegaly, or an elevated left hemidiaphragm—is poor.

Bilateral anterothoracosternotomy (clamshell procedure) allows excellent exposure of both hemithoraces, including the left lower lobe, although some surgeons think this incision is morbid due to severe postoperative pain.

Posterolateral thoracotomy allows excellent visualization of one hemithorax. However, this approach necessitates a second-stage operation when treating bilateral metastases, usually performed about 2 to 4 weeks after the first surgery.

VATS resection offers a well-tolerated and effective approach for limited-volume and relatively superficial lesions. Pleural-based lesions are therefore easily visualized and excised. Unfortunately, the ability to carefully evaluate the parenchyma for deeper or smaller nonvisualized lesions is poor, and some reports suggest an increased risk of local recurrence with thoracoscopy, likely due to intraoperative tumor rupture, especially in sarcomas.

At surgery, wedge resections with a 1-cm margin are preferred. Using staplers that allow the specimen side to be staple-free enhances the pathologist's ability to adequately examine the true parenchymal margin. If multiple nodules residing within one segment, lobe, or lung preclude resection with multiple wedges, then laser or cautery resections ("lumpectomy") can be performed. Anatomical resection can be used when central lesions are resected but should be performed carefully since the likelihood of recurrence is high; every effort should be made to preserve lung parenchyma.

Chemotherapy and Radiation as Adjuvant Treatment for Pulmonary Metastases

The role of radiation therapy for pulmonary metastases is limited to the palliation of symptoms of advanced lesions with extensive pleural, bony, or neural involvement, although SBRT has recently gained traction in the management of pulmonary metastases from colon cancer. The value of chemotherapy preoperatively or postoperatively in metastatic clinical situations is dependent on the specific disease process and its biology. Chemotherapy is generally indicated in the metastatic setting to treat any potential microscopic disease deposits and determine the biology of the disease. Disease progression on chemotherapy is usually associated with poor outcome, even after local control of metastases.

Surveillance

The frequency and intensity of follow-up after resection are determined by the primary tumor but usually involve CT scans.

NEOPLASMS OF THE MEDIASTINUM

The mediastinal compartment can harbor numerous lesions of congenital, infectious, developmental, traumatic, or neoplastic origin. With current imaging options, much can be learned about mediastinal masses from CT scans and MRIs. Biopsy should be performed on all but selected smaller mediastinal masses, which may be completely resected without prior biopsy. Surgical resection is a feasible first step for small (<4 cm) tumors that have characteristics of thymoma on imaging and when a surgeon believes that complete R0 resection can be achieved. Otherwise, histologic diagnosis is beneficial before initiation of treatment to avoid incomplete surgical resections of tumors such as thymoma, thymic carcinoma, germ

cell tumors, or lymphoma. With the advent of VATS and robot-assisted surgery, many mediastinal masses can be resected without sternotomy. Skill and patient selection is important in the success of these procedures.

Pathology

A study combining nine previous series was performed to better approximate the true incidence of mediastinal lesions (Table 7.4). In adults, neurogenic and thymic tumors contribute 23% and 19%, respectively, to the overall incidence, whereas in children they contribute 39% and 3%, respectively. This section does not attempt to describe the myriad cystic and other rare miscellaneous lesions but instead concentrates on the more common diagnoses.

Diagnosis

Mediastinal lesions are most commonly asymptomatic. When symptoms do occur, they result from compression of adjacent structures or systemic endocrine or autoimmune effects of the tumors. Children, with their smaller chest cavities, tend to have symptoms at presentation (two-thirds of children vs. only one-third of adults) and more commonly have malignant lesions (greater than 50%). Symptoms can include cough, stridor, and dyspnea (more common in children), as well as symptoms of local invasion such as chest pain, pleural effusion, hoarseness, Horner syndrome, upper-extremity and back pain, paraplegia, and diaphragmatic paralysis. Most symptoms are nonspecific with regard to the tumor histology with the exception of myasthenia gravis, which is strongly suggestive of thymoma.

TABLE 7.4 Overall Incidence of Mediastinal Tumors

Thymic	19 (3)[a]
Neurogenic	23 (39)[a]
Lymphoma	12
Germ cell	12
Cysts	18
Mesenchymal	8
Miscellaneous	8

[a]Numbers in parentheses represent incidence in children.

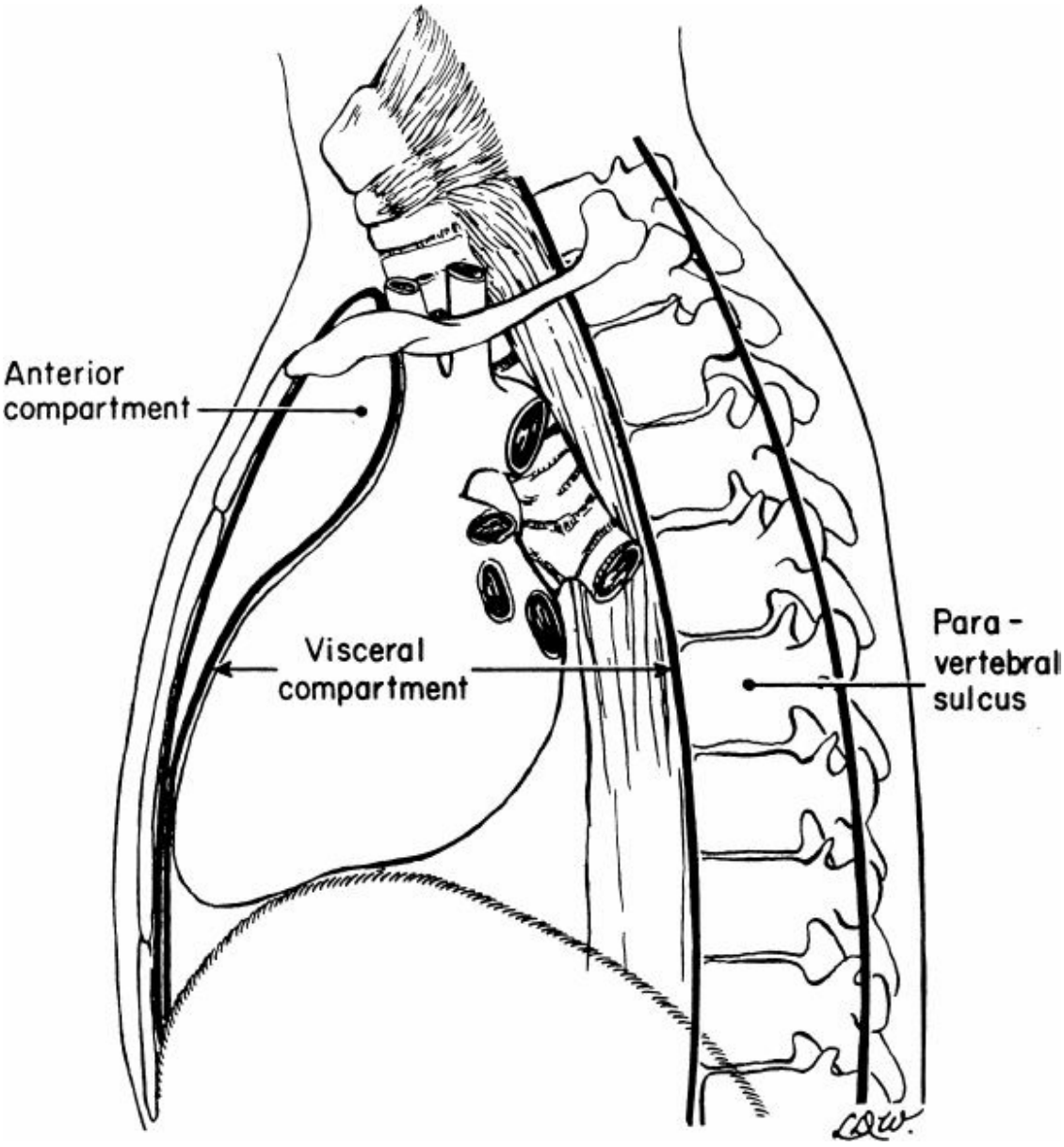


Figure 7.5 Anatomical boundaries of mediastinal masses according to one commonly used classification.

Fifty percent of lesions are diagnosed by CXR. The position of the tumor within the mediastinum on lateral projection can help tailor the

differential diagnosis (Fig. 7.5, Table 7.5). The standard for further assessment of the lesion is contrast CT. Certain tumors and benign conditions can be diagnosed or strongly suggested by their appearance on CT scans. Angiography or MRI may be required if a major resective procedure is planned and vascular involvement suspected. Nuclear imaging such as thyroid and parathyroid scanning, gallium scanning for lymphoma, and metaiodobenzylguanidine scanning for pheochromocytomas may also be indicated. The use of serum markers is mandatory in the diagnosis of germ cell and some rare neuroendocrine tumors.

FNA and a transthoracic core needle biopsy should be performed for most tumors, although the diagnosis of lymphoma may require larger amounts of tissue for tumor typing. Extended mediastinoscopy, VATS, or the Chamberlain procedure may aid in the diagnostic process. Sternotomy or thoracotomy should be exceedingly rare for a tissue diagnosis.

Tumor Types and Their Treatment

Therapy, like staging, is determined by the type of tumor and its histologic characteristics (Table 7.6).

TABLE 7.5 Usual Location of Common Primary Tumors and Cysts of Mediastinum

Anterior Compartment	Visceral Compartment	Paravertebral Sulci
Thymoma	Enterogenous cyst	Neurilemmoma (schwannoma)
Germ cell tumors	Lymphoma	Neurofibroma
Lymphoma	Pleuropericardial cyst	Malignant schwannoma
Lymphangioma	Mediastinal granuloma	Ganglioneuroma
Hemangioma	Lymphoid hamartoma	Ganglioneuroblastoma
Lipoma	Mesothelial cyst	Neuroblastoma
Fibroma	Neuroenteric cyst	Paraganglioma
Fibrosarcoma	Paraganglioma	Pheochromocytoma
Thymic cyst	Pheochromocytoma	Fibrosarcoma
Parathyroid adenoma	Thoracic duct cyst	Lymphoma
Aberrant thyroid		

Neurogenic tumors include schwannoma, neurofibroma, ganglioneuroblastoma, neuroblastoma, pheochromocytoma, and

paraganglioma. They are the most common tumors arising in the posterior compartment. Complete surgical resection is generally curative, except in highly malignant tumor subtypes, which may require additional therapy depending on the histologic findings.

Thymoma arises from thymic epithelium, although its microscopic appearance is a mixture of lymphocytes and epithelial cells. Thymomas are classified as lymphocytic (30% of cases), epithelial (16%), mixed (30%), and spindle cell (24%). Histologic evidence of malignancy is difficult to obtain because benign and malignant lesions can have similar histologic and cytologic features. Surgical evidence of invasion at the time of resection is the most reliable method of differentiating between malignant and benign thymomas. Completeness of resection is the best predictor of survival, and when complete resection cannot be performed, adjuvant radiation therapy is used. Neoadjuvant chemotherapy has also been demonstrated to be beneficial, especially in tumors >4 cm in diameter, however it is not uniformly used.

Lymphomas make up approximately 50% of childhood and 20% of adult anterior mediastinal malignancies. They are treated nonsurgically but may require surgical biopsy to secure a diagnosis.

Germ cell tumors comprise teratomas, seminomas, and nonseminomatous germ cell tumors. Teratomas, the most common type, are typically benign and are treated with surgical resection. Malignant teratomas are very rare and are often widely metastatic at diagnosis. Seminomas progress in a locally aggressive fashion and are both chemosensitive and radiosensitive. Nonseminomatous malignant tumors include embryonal carcinoma and choriocarcinoma, both of which carry a poor prognosis, and the more favorable endodermal sinus tumor. Chemotherapy is the first-line and second-line option for nonseminomatous germ cell tumors, to the point of normalization of tumor markers. Surgical resection is indicated for any residual mass, which is usually comprised of the remaining teratoma component of the tumor.

TABLE 7.6 Frequency and Treatment of Malignant Chest Wall Tumors

Cell Type	Estimated Frequency (%)	Standard Therapy
Chondrosarcoma	35	Surgical resection
Plasmacytoma	25	Radiation + chemotherapy
Ewing sarcoma	15	Surgery + chemotherapy
Osteosarcoma	15	Surgery + chemotherapy
Lymphoma	10	Chemotherapy ± radiation

Miscellaneous cysts and mesenchymal tumors include thyroid goiters, thyroid malignancies, mediastinal parathyroid adenomas, bronchogenic cysts, pericardial cysts, duplications, diverticula, and aneurysms. Surgical resection is used for the all these diagnoses.

Surveillance

The frequency and intensity of follow-up after resection are determined by the primary tumor. CXR remains the mainstay of surveillance, with CT scanning reserved for evaluation subsequent to abnormal CXR findings.

NEOPLASMS OF THE CHEST WALL

Primary chest wall malignancies account for less than 1% of all tumors and include a wide variety of bone and soft-tissue lesions. The absence of a large series makes the prospective evaluation of treatment options difficult. As more patients with these tumors are treated at large referral institutions, the initiation of multi-institutional databases may help settle some of the more controversial aspects of therapy; conduction of clinical trials will likely not be feasible.

Pathology

Primary chest wall tumors include chondrosarcoma (20%), Ewing sarcoma (8% to 22%), osteosarcoma (10%), plasmacytoma (10% to 30%), and, infrequently, soft-tissue sarcoma. Chondrosarcomas arise from the ribs in 80% of cases and from the sternum in the remaining 20%. They are related to prior chest wall trauma in 12.5% of cases and are very resistant to radiation and chemotherapeutic agents. Ewing sarcoma is part of a spectrum of disease having primitive neuroectodermal tumors at one end and Ewing sarcoma at the other. Multimodality therapy, including both radiation therapy and chemotherapy, has been shown to be beneficial for this tumor. Osteosarcomas are best treated with neoadjuvant therapy, with

prognosis being predicted by the tumor's size, grade, response to chemotherapy, and completeness of resection. Solitary plasmacytoma confined to the chest must be confirmed by evaluating the remaining skeletal system. Surgery can then be used to confirm the diagnosis. If radiation therapy is unable to achieve local control, then resection may be indicated. Soft-tissue sarcomas are rare and are primarily resected. Adjuvant therapy is based on specific histologic findings.

Diagnosis

Chest wall tumors are asymptomatic in 20% of patients, whereas the remaining 80% present with an enlarging mass. A total of 50% to 60% of these patients will have associated pain. Radiographic assessment usually includes CXR and CT; however, MRI is being used instead of CT with increasing frequency because of its ability to image in multiple planes with superior anatomical distinction. Pathologic diagnosis is made by FNA (64% accuracy) or core biopsy (96% accuracy). Incisional biopsies, if necessary, should be carefully planned to allow complete excision of the scar and the tumor during the definitive procedure.

Staging

Chest wall lesions are staged according to the primary tumor identified. Sarcomas are staged based on tumor size and grade.

Treatment

As outlined previously, the treatment of chest wall lesions is determined by the diagnosis. Most, with few exceptions, require resection as part of the treatment. Posterior lesions covered by the scapula or that require resection of less than two ribs do not require reconstruction of the chest wall. However, all other, mainly anterior, defects require some form of stable reconstructive technique. A simple mesh closure using Marlex, Prolene, or Gore-Tex mesh is acceptable as long as the material is secured in position under tension. A more rigid prosthesis is methyl methacrylate sandwiched between two layers of Marlex mesh. Sternal- and rib-plating systems exist to enhance stabilization of a rigid repair. Our recent study comparing pulmonary and infectious outcomes after chest wall reconstruction with flexible or rigid prosthesis did not identify significant

differences between these two techniques. The pulmonary complication rate increased with the number of resected ribs, and there was a bias toward more rigid prosthesis use with larger defects.

If the chest wall lesion involves the overlying muscle or the skin, a large defect may be present after resection. This may require a muscle or myocutaneous flap, especially if the field was or will be irradiated.

Surveillance

Once treated and in remission, chest wall tumors tend to recur either locally or with pulmonary or hepatic metastases. Regular follow-up with careful examination and CT scanning should suffice to monitor all significant sites of recurrence.

NEOPLASMS OF THE PLEURA

There are two main types of pleural neoplasms. The first, malignant pleural mesothelioma, remains an uncommon and highly lethal tumor with no adequate method of treatment. It behaves as a locally aggressive tumor in half of patients and the other half develop distant metastatic disease. Its relationship with asbestos exposure was suggested in the 1940s and 1950s and clearly established in 1960. The second, a more localized pleural tumor known as solitary fibrous tumor (SFP) is generally benign; however, malignant variants exist. Complete resection is usually curative, although malignant SFP is known to recur. Prolonged survival with disease is at times possible due to the lesser tumor aggressiveness compared with mesothelioma.

Pathology

Localized mesotheliomas and malignant SFPs of the pleura are very rare. There is some controversy as to whether these lesions are even mesothelial at all because no epithelial component may be identifiable. More commonly, a benign SFP of the pleura is found. However, diffuse pleural mesothelioma is always a malignant process. There are decades of latency before the development of this disease after exposure to asbestos. The incidence of this disease reflects the widespread use of asbestos in the 1940s and 1950s, and the presence of mesothelioma will still continue because mechanisms for limiting occupational asbestos exposure were not

instituted until the 1970s. Mesothelioma commonly presents as an epithelial histology and less commonly as a very aggressive sarcomatoid or mixed histology. It can be hard to differentiate this lesion from metastatic adenocarcinoma to the pleura. Immunohistochemical analysis, electron microscopy, and calretinin staining, however, have aided in establishing the diagnosis.

Diagnosis

The presentation of mesothelioma is often vague and nonspecific, with dyspnea and pain common in 90% of patients. Radiographic diagnosis in the early stage is often difficult, with the findings limited to a pleural effusion in many cases. Even CT may fail to identify any other abnormalities at this stage. The classic finding of a thick, restrictive pleural rind is a late finding. Thoracentesis is diagnostic in 50% of patients and pleural biopsy is positive in 33%. If the diagnosis remains elusive, thoracoscopy is diagnostic in 80% of patients.

Staging

A staging system for diffuse malignant pleural mesothelioma was initially proposed by Rusch and the International Mesothelioma Interest Group (IMIG).The most recent staging system can be found in the *AJCC Cancer Staging Manual*, eighth edition.

Treatment

The treatment of mesothelioma continues to evolve. Attempts at radical resections, such as extrapleural pneumonectomy or pleurectomy and decortication, have led to some improvements in local control, but have had only a limited impact on survival at the cost of a significantly increased operative risk. The addition of adjuvant radiation therapy has increased local control. Although the removal of the entire lung facilitates radiation delivery, novel intensity modulated radiation therapy (IMRT) techniques have allowed for adjuvant radiation even after pleurectomy and decortication. The only therapy that has been demonstrated to improve survival in mesothelioma, albeit for 3 additional months, has been chemotherapy consisting of cisplatin and pemetrexed, administered in a randomized trial. The median survival from the time of diagnosis in

untreated patients ranges between 6 and 9 months. With trimodality therapy (see the following paragraph), the median survival has been extended to 17 to 20 months; however, this has been at the cost of multiple cycles of chemotherapy, gruesome surgery, and 5 to 6 weeks of adjuvant radiation therapy totaling approximately 6 months of intensive treatment.

In patients suitable for aggressive trimodality therapy, we begin with both image-based and invasive staging with mediastinal node sampling and diagnostic laparoscopy. Patients then undergo up to four cycles of platinum and pemetrexed chemotherapy followed by surgical resection with either extrapleural pneumonectomy or pleurectomy decortication. The decision about the type of surgical procedure is based on physiologic reserves and intraoperative nodal sampling status, reserving extrapleural pneumonectomy only for node-negative patients. Adjuvant IMRT then completes the trimodality regimen.

Surveillance

CT scans every 6 months are required to detect recurrences or monitor residual disease. Unfortunately, treatment options are limited, although some phase I trials are demonstrating encouraging results in anecdotal cases. The role of immunotherapy in mesothelioma has not yet been defined, but clinical trials in this setting are forthcoming.

Recommended Readings

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8 Esophageal Carcinoma

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INTRODUCTION

In the United States and other western societies, cancer of the esophagus is relatively uncommon, representing only a small percentage of newly diagnosed invasive malignancies. However, it is the eighth most common malignancy worldwide comprising approximately 4% of the newly diagnosed tumors per year. It is highly virulent, similar to other malignancies such as lung or pancreas. The yearly incidence of esophageal cancer is comparable to its yearly total of cancer-related deaths. Treatment paradigms are individualized and are primarily related to clinical stage at presentation. Although surgical resection has traditionally been the mainstay of therapy, most newly diagnosed cancers present at a late stage and are therefore precluded from curative resection. Symptoms such as dysphagia, weight loss, regurgitation, or back pain are alarming as they potentially herald advancing disease. Those patients who have been fortunate to have their disease discovered at a very early stage may be candidates for esophageal sparing mucosal resections or esophagectomy. Patients with locally advanced tumors will typically undergo multimodality approaches that combine concurrent chemoradiation followed by reevaluation for surgery. These approaches have resulted in 5-year survival rates of 40% to 75% in the subset of patients who have a complete or near complete pathologic response after preoperative therapy. Finally, patients who present with advanced disease are treated with palliative measures, which include chemotherapy, radiation, mechanical devices such as stents and/or feeding tubes, and supportive care.

EPIDEMIOLOGY

According to the National Cancer Institute database for 2016, there will be an estimated 16,910 new cases of esophageal cancer diagnosed in the

United States, and 15,690 will die of the disease. Data provided on the SEER web site indicate an 18.6% 5-year overall survival and relatively consistent incidence of events and mortality since data began being tracked from 1991 to 2016. In the past, squamous cell carcinomas (SCCs) accounted for more than 95% of cases, but in recent years, adenocarcinoma arising in the background of Barrett esophagus has become increasingly more common, and it now accounts for more than 75% of the esophageal cancers at most major American centers. Esophageal carcinoma, particularly SCC, has substantial geographic variation, from 1.5 to 7 cases per 100,000 people in most parts of the world, including the United States, to 100 to 500 per 100,000 people in its endemic areas such as northern China, South Africa, Iran, Russia, and India. Males have a two- to threefold higher overall risk than females, and a seven- to tenfold higher risk for the development of adenocarcinoma. Furthermore, in the United States, SCC is approximately five times more common among African Americans than it is among whites, whereas adenocarcinoma occurs approximately three to four times more often in whites, particularly in men. Thankfully, SCCA among African American males has been on a sharp decline in the past two decades. Both major histologic types are rare in patients younger than 40 years, but the incidence increases thereafter.

ETIOLOGY AND RISK FACTORS

Several different environmental and genetic risk factors have been identified as potential causes of esophageal cancers, particularly SCC. A well-established risk factor is the combination of smoking and alcohol consumption which has a synergistic effect on the development of esophageal SCC, increasing the risk by as much as 44 times. Other risk factors or associations for esophageal SCC include SCC of the head and neck (presumably because of the risk associated with alcohol and smoking), achalasia (as high as 30 times increased risk), strictures resulting from ingestion of caustic agents such as lye, Zenker diverticulum, esophageal webs in Plummer–Vinson syndrome, prior radiation, and familial connective tissue disorders such as tylosis (50% have cancer by 45 years). In geographic areas where esophageal SCC reaches epidemic levels, such as in China, definitive risk factors other than the typical causative agents listed above, are currently unknown. Some risk factors may include diets that are deficient in vitamins A, C, riboflavin, and

protein, and have excessive nitrates and nitrosamines. Fungal contamination of foodstuffs with the associated aflatoxin production may be another important risk factor outside of western societies.

For adenocarcinoma, the typical patient is a middle class, over-weight male in his 60s or 70s. The primary etiologic factors are obesity and Barrett esophagus, with an estimated annual incidence of malignant transformation of approximately 0.5%/year, representing 125 times greater risk than that in the general population. This risk seems to be mediated through reflux disease. Esophageal adenocarcinomas are known to progress through a metaplasia–dysplasia–cancer sequence, similar to colon cancers. Gastroesophageal reflux disease results in the overexposure of the esophageal mucosa to acid and bile. Specifically, the conjugated bile salts (secondary bile acids) are believed to synergistically damage the mucosa, leading to increased DNA methylation and variations in ploidy (as well as other genetic and molecular changes) and the formation of intestinal metaplasia (Barrett mucosa) or cardiac metaplasia. Both are recognized as precursor lesions to esophageal/gastroesophageal junction cancers. Tobacco use and the eradication of *Helicobacter pylori* are also linked to the increased incidence of esophageal adenocarcinoma in the United States.

PATHOLOGY

Esophageal cancer is seen in two main histologic types: SCC and adenocarcinoma. In the United States, approximately 20% of cases of SCC involve the upper third of the esophagus, 50% involve the middle third, and the remaining 30% extend from the distal part of the esophagus to the gastroesophageal junction. SCC rarely invades the stomach, and there is usually a discrete segment of normal mucosa between the cancer and the gastric cardia. In contrast, nearly 97% of adenocarcinomas develop in the middle and distal esophagus, and many extend into the stomach if they are centered near the gastroesophageal junction. Cancers arising in Barrett esophagus are believed to comprise upward of 50% to 70% of all adenocarcinomas involving the distal esophagus and gastroesophageal junction. They can vary in length and range in contour from flat, infiltrative lesions to fungating, polypoid masses. Ulceration is often present and may even be deep enough to cause perforation. Because symptoms appear late in the progress of the disease, the typical esophageal carcinoma is a circumferential, exophytic, fungating mass that is nearly or

completely transmural. Early access to the submucosal lymphatics allows tumors to spread freely along a submucosal plane and present with very long tumors or multiple mucosal lesions. Similarly, early metastases to lymph nodes or distant sites are common. This is because there is a rich submucosal lymphatic system that tumors may infiltrate at a very early period of growth. This lymphatic system leads directly to the blood stream by way of the thoracic duct, facilitating early dissemination of disease. Microscopically, adenocarcinomas can resemble cells of the gastric cardia or colon, and most are well or moderately differentiated. Signet ring differentiation may signify a gastric cardia origin, but this is not an absolute rule.

Other less common primary malignant neoplasms of the esophagus include neuroendocrine tumors, gastrointestinal stromal tumors, variants of SCC or adenocarcinomas (e.g., adenosquamous), melanomas, sarcomas, and lymphomas.

CLINICAL FEATURES

Clinical presentation is generally insidious, and typical symptoms occur late in the course of the disease, usually precluding an easy cure. Most patients experience symptoms for 2 to 6 months before they seek medical attention. The most common symptom is progressive dysphagia, which occurs in as many as 80% to 90% of patients. This is usually a late sign because the esophageal lumen must be reduced to 50% to 75% of its original size before patients experience this symptom. Typically, malignant dysphagia will begin when the esophageal functional diameter approaches 12 to 13 mm. Weight loss is also common, with an estimated mean weight loss of 10 kg from the onset of symptoms. This sign is also an independent predictor of poor outcome, as is presentation with advanced stage. Other symptoms include varying degrees of odynophagia (in approximately 50%), as well as emesis, cough, regurgitation, anemia, hematemesis, and aspiration pneumonia. Hoarseness can be due to invasion of the recurrent laryngeal nerve, and Horner syndrome indicates invasion of the sympathetic trunk. Hematemesis and melena usually indicate friability of the tumor or its invasion into major vessels. Bleeding from the tumor mass occurs in 4% to 7% of patients and may cause considerable difficulty with treatment.

DIAGNOSTIC EVALUATION

Results of the physical examination may depend in large part on the degree of weight loss and cachexia. Enlarged cervical or supraclavicular lymph nodes can be biopsied with fine-needle aspiration (FNA) and are indicative of advanced disease. In the past, there was significance placed on plain CXR, barium swallow studies, and bone scans. However, these have been replaced by modern imaging. Computed tomography (CT) scans of the chest and abdomen should be obtained to assess the degree of any local invasion of mediastinal structures, adenopathy, or for evidence of dissemination/distant metastasis, especially in the lungs.

In addition to a high-resolution CT scan, integrated positron emission tomography (PET) is being used in the diagnostic staging algorithm. It has been shown to alter the treatment course in approximately 15% of patients with locally advanced tumors, which in itself has rendered it cost efficient. This modality is helpful in determining the significance of nonregional adenopathy or distant lesions and may carry prognostic information in terms of the level of initial nucleotide uptake and midterm response to preoperative treatment. It is also very efficient at detecting bone-related metastases and has primarily replaced the use of bone scans. As PET–CT is not sensitive for brain evaluation, any neurologic signs or complaints (e.g., headaches, visual disturbances, and new onset weakness) should be assessed with magnetic resonance (MR) imaging (preferred) or CT scan of the brain.

Upper endoscopy is currently the most widely used technique for the diagnosis and staging of esophageal cancer. Flexible endoscopy allows magnified visual observation and histologic sampling of the esophagus, as well as visualization of the stomach. A detailed description of tumor location within the esophagus and stomach is critical to surgical and radiation treatment planning. Biopsy and brush cytology can produce diagnostic accuracy of nearly 100% with adequate sampling, and gentle endoscopic dilation of tight strictures can be performed by experienced endoscopists to allow passage of the endoscope beyond the tumor. The addition of endoscopic ultrasound (EUS) should be used to assess the T and N status of the lesion. EUS is most accurate in predicting the depth of invasion of the primary lesion, and this can provide very good insight into the potential of surrounding organ or lymph node involvement. Regional lymph nodes in the mediastinal, paraesophageal, paragastric, porta hepatis, and celiac areas are routinely identified and can be biopsied via

transesophageal or bronchoscopic ultrasound-guided aspiration (FNA) for diagnosis. Tumors that involve the upper or middle third of the esophagus should be evaluated by flexible and/or rigid bronchoscopy to rule out tracheobronchial involvement.

STAGING

The staging system of the American Joint Committee on Cancer (AJCC) uses the TNM classification and is the most commonly used system in the United States (Table 8.1). Although CT scanning is probably the most widely used noninvasive staging modality worldwide, its accuracy is quite limited. Overall accuracy in determining resectability and T status have been estimated at 60% to 70%, whereas accuracy in determining N status is generally less than 60%. Accuracy in the detection of metastatic disease is somewhat better, estimated at 70% to 90% for lesions larger than 1 cm. The use of combined imaging with PET–CT has improved the accuracy of both tests. The ability to combine anatomical irregularity to areas of abnormal fluorodeoxy glucose uptake on a superimposed CT image increases the predictive value over PET alone or CT alone. Studies with this technique have reported overall accuracy levels of nearly 60% and 90% in the ability to detect both locoregional nodal metastases and distant diseases, respectively.

EUS is probably the most accurate means currently available for determining T and N status. Reported overall accuracy for depth of invasion is 76% to 90%; overall accuracy in predicting resectability is approximately 90% to 100% for adenocarcinoma, but decreases to 75% to 80% for SCC. Studies comparing EUS and CT scanning generally agree that EUS is superior in determination of overall T status and assessment of regional lymph nodes (70% to 86% accuracy). The precise differentiation between benign and malignant nodes occasionally remains problematic, however, due to micrometastases that are undetectable by EUS and enlarged inflammatory lymph nodes that are incorrectly classified as metastatic. FNA can be helpful in making this diagnosis. Minimally invasive techniques such as thoracoscopy and laparoscopy may also be utilized in the staging of esophageal cancer. Thoracoscopy allows visualization of the entire thoracic esophagus and the periesophageal nodes, when performed through the right hemithorax, or the aortopulmonary and periesophageal nodes and the lower esophagus, when performed through the left chest. Lymph nodes can be sampled for

histologic evaluation, the pleura can be examined, and adjacent organ invasion (T4) can be confirmed. The overall accuracy for detecting lymph node involvement has been reported to be as high as 81% to 95%. Laparoscopy and laparoscopic ultrasonography are useful in evaluating the peritoneum, liver, gastrohepatic ligament, gastric wall, diaphragm, and the perigastric and celiac lymph nodes. Biopsies and peritoneal washings can be performed to confirm nodal or metastatic disease. These modalities are especially useful in patients with gastroesophageal junction or proximal gastric tumors. In addition, a feeding jejunostomy can be placed for nutritional support before treatment begins. Studies have suggested that the overall accuracy of laparoscopy in staging and determination of resectability in esophageal cancer is as high as 90% to 100% and that invasive staging procedures may prevent unnecessary surgical resection in as many as 20% of patients. Prospective comparisons with CT and EUS have suggested that laparoscopy and laparoscopic ultrasonography have superior overall accuracy in staging, particularly for lymph nodes and metastatic diseases. Mediastinoscopy can also prove helpful in assessing regional lymph nodes at the right and left paratracheal lymph node stations, along the mainstem bronchi, in the aortopulmonary window, or in the subcarinal area.

TABLE 8.1 TNM Staging for Esophageal Cancer

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria, muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, and trachea

Regional Lymph Nodes (N)

Nx	Regional nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage	T	N	M	Grade	Tumor Location[a]
Squamous Cell Carcinoma					
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any

IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Adenocarcinoma					
0	Tis (HGD)	N0	M0	1, X	
IA	T1	N0	M0	1–2, X	
IB	T1	N0	M0	3	
	T2	N0	M0	1–2, X	
IIA	T2	N0	M0	3	
IIB	T3	N0	M0	Any	
	T1–2	N1	M0	Any	
IIIA	T1–2	N2	M0	Any	
	T3	N1	M0	Any	
	T4a	N0	M0	Any	
IIIB	T3	N2	M0	Any	
IIIC	T4a	N1–2	M0	Any	
	T4b	Any	M0	Any	
	Any	N3	M0	Any	
IV	Any	Any	M1	Any	

[a]Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.
Adapted from the AJCC Cancer Staging Manual, 8th edition, Springer International Publishing AG Switzerland, 2017.

TREATMENT

Treatment options vary according to presenting stage, patient performance status, and local expertise.

Stage 0–I

Patients with in situ carcinoma (high-grade dysplasia, HGD) or tumors that are limited to the mucosa (stages 0 and I) may be candidates for esophageal-preserving techniques of endoscopic resection and ablation. This modality is typically limited to patients with smaller lesions (~2 cm) located within the mucosa generally penetrating no more deeply than the muscularis mucosae. Favorable factors include ability to completely resect, well–moderate differentiation, and no evidence of lymphovascular invasion. Patients with disease beyond the very superficial submucosa, or those with endoscopically unresectable lesions, or with evidence of poor differentiation and LVI should be considered for formal surgical resection if medically fit. Because accurate clinical staging of early-stage disease is

difficult, patients in whom there is a question of depth of mucosal invasion should be considered for a diagnostic endoscopic mucosal resection (EMR) at a center of expertise with high volume. Confirmation of very early stage may result in a therapeutic organ-preserving endoscopic resection. Tumors found to be more deeply invasive (stages I, T1b) may not be amenable to definitive EMR but have a lower risk of metastatic lymphadenopathy and should be considered for curative resection. EMR helps to differentiate watershed staging overlaps that will significantly alter the therapeutic recommendations. For example, T1a versus T1b can be difficult to differentiate on EUS, and similarly the treatment paradigm between T1 and T2 would be very different.

Stage II–III

Tumors that invade more deeply harbor a higher probability of regional lymph node involvement. In fact, there is a direct correlation of depth of invasion to lymph node involvement, where deep submucosal lesions have approximately a 30% risk of regional lymphadenopathy and transmural tumors carry risk of 80% to 100%. Because results with surgery alone in patients with regional lymph node metastasis are relatively poor, clinical studies began to focus on including multimodality treatment in conjunction with surgery. Recent randomized trials with locally advanced disease have shown a survival advantage in groups treated with neoadjuvant chemoradiation followed by surgery compared to those treated with surgery alone. However, debate continues regarding the most appropriate treatment of a clinically staged T2N0 patient. Many argue for surgery followed by selective chemoradiation based on surgical pathology. This approach is supported by both retrospective and some prospective data. However, an equally compelling argument stands with the same level of evidence that preoperative staging is inaccurate in many patients, resulting in upstaging in approximately 40% of operated patients from N0 to N+ status. These data prompt some groups to advocate for neoadjuvant treatment at centers of excellence, where therapy including surgery can be given with very low (2% to 3%) 30-day mortality and good overall survival.

There is little debate that locally advanced adenocarcinoma, stage IIb and III diseases, should be treated with concurrent neoadjuvant chemoradiation followed by restaging and consideration for surgical resection. Squamous cancers are increasingly being treated with definitive

chemotherapy and radiation, especially those located in the cervical and very proximal esophagus. Treatment for SCCA tumors located in the mid-distal esophagus is often individualized. Two European trials (Bedenne, 2007; Stahl, 2005) have shown statistical survival equipoise in groups treated with definitive chemoradiation versus chemoradiation plus surgery if they responded to therapy. However, both of these trials suffered from excessive mortality in the surgical arm, and DFS was significantly favored in the surgical arm of one trial. Nonetheless, in patients with SCCA of the esophagus who have had a clinical complete response to therapy there are advocates for observation rather than surgical resection; a decision our group bases on individual cases. Nonresponding patients and those with tumor behind the airway should be considered for resection, based on presence of disease and high-risk recurrence areas.

Stage IV

Patients who present with nonregional lymph node involvement or other distant metastatic disease are candidates for palliative chemotherapy. On occasion, patients with stage IV disease whose tumor burden is systemically controlled become candidates for consolidative local regional therapy (chemoradiation). As there is a significant morbidity and mortality incidence associated with palliative surgical resections, this procedure is generally not recommended unless a patient has uncontrolled bleeding or perforation and would otherwise be expected to have a significant life span despite metastatic or advanced esophageal cancer. Given this, there are also nonoperative methods of controlling these complications such as mechanical stents for perforation or trachea–esophageal fistula and radiation for local control of bleeding. The concept of adding surgery in oligometastatic disease that is well controlled over a period of time is gaining some traction.

Operative Approaches

There are many available techniques for performing esophageal resection, and most often this choice is based on surgeon preferences and/or tumor location. Esophageal tumors located distally or at the gastroesophageal junction can be managed by subtotal esophagectomy, esophagogastrectomy, or segmental esophagectomy with bowel interposition. The extent of gastric and esophageal involvement, as well as

the stage of the primary tumor, should guide the surgeon to an appropriate approach. A subtotal esophagectomy through a right thoracotomy and laparotomy (Ivor Lewis or Tanner–Lewis esophagectomy) allows for generous resection of the stomach because the esophageal reconstruction takes place in the chest at or above the level of the azygos vein. Locally advanced tumors with involvement of the distal esophagus and proximal stomach lend themselves to this approach because a lymphadenectomy is easily performed in two fields and negative margins can be obtained on the stomach with less concern for gastric necrosis. However, tumors with extensive involvement of the stomach and esophagus may require an esophagogastrectomy, with interposition of small or large bowel for reconstruction. Early distal tumors or short-segment Barrett esophagus with HGD should be treated endoscopically, though a rare patient may not have a salvageable esophagus due to extent of disease, superficial though it may be. These can be treated with standard esophagectomy, segmental esophagectomy with small bowel interposition (Merendino procedure), or vagal-sparing esophagectomy with gastric or bowel interposition.

Proximally located (e.g., upper and midesophageal) tumors often require a total esophagectomy because it is difficult to achieve negative margins with segmental or subtotal resections (e.g., Ivor Lewis esophagectomy). Given the propensity for esophageal cancers to spread in the submucosal lymphatic system, it is recommended that a minimum of a 5-cm margin, and preferably a 10-cm margin, be taken on the esophagus. This is a critical decision-making factor when formulating a treatment algorithm for an individual patient. The two most popular methods to achieve a total or near-total esophagectomy differ according to whether thoracotomy is used for esophageal mobilization. The esophagus can be mobilized using a right thoracotomy with the conduit brought either through the posterior mediastinum (preferred) or substernally to the neck for anastomosis (McKeown or three-field approach). Alternatively, a transhiatal esophagectomy can be performed with mobilization of the intrathoracic esophagus from the esophageal hiatus to the thoracic inlet without the need for thoracotomy. The advantage of the transhiatal technique is that it avoids thoracotomy while achieving a complete removal of the esophagus. The potential disadvantages of this technique include a limited periesophageal and mediastinal lymphadenectomy, the risk of causing tracheobronchial or vascular injury during blunt dissection of the esophagus, and significantly higher locoregional recurrence rates. In

addition, the use of a cervical anastomosis is associated with a higher rate of anastomotic leakage than an intrathoracic anastomosis (12% vs. 5%, respectively) although the morbidity may be less with a cervical leak than it is with a thoracic leak. Other potential downsides to a cervical anastomosis include pharyngeal reflux, nocturnal aspiration, prolonged swallowing dysfunction after surgery, and an increased incidence of recurrent laryngeal nerve palsy. This last complication is underestimated in its importance; a patient with an intrathoracic stomach and limited ability to protect his/her airway is at great danger in the immediate postoperative period and is also in chronic danger of aspiration. On the other hand, intrathoracic anastomoses are hampered by a higher reoperation incidence when there is a postoperative anastomotic leak (about 4% to 10%).

Patients who present with cervical esophageal carcinomas have several treatment options. Advances in chemoradiotherapy have relegated resection of most localized cervical lesions to salvage procedures. Patients who have persistent locoregional, limited disease after definitive medical therapy are candidates for segmental resections with immediate or delayed reconstruction. Small bowel, neck, or musculocutaneous free flaps are well suited to esophageal reconstructions in the cervical area, with or without pharyngolaryngectomy. An alternative option for patients with early-stage disease is immediate resection and reconstruction. At the other end of the spectrum, lengthy lesions with involvement into the thoracic esophagus may require a complete esophagectomy via a three-field approach.

Extent of Resection/Lymphadenectomy

Although it is generally agreed that surgical resection has a therapeutic role in the treatment of local and locoregional disease, great controversy remains over the extent of the resection necessary and over the value and extent of lymphadenectomy. There is one group of thought that lymph node metastases are markers for systemic disease and that removal of involved nodes in most cases offers no survival benefit. This is very likely to be true when more than six lymph nodes are involved with cancer on the surgical specimen. However, many well-respected and experienced surgeons believe that some patients with affected lymph nodes can be successfully cured with an aggressive surgical approach that focuses on wide peritumoral excision and extended lymphadenectomy using a transthoracic/thoracoabdominal and cervical approach (en bloc or radical esophagectomy). There is currently no definitive evidence to support the

superiority of either philosophy; however, many collaborative, multi-institutional reports that have focused on specific subsets of patients in stages IIb to III have shown that patients who have undergone complete lymphadenectomy have improved survival and can still look forward to excellent locoregional control. Proponents of radical resection have reported increased survival rates with more extensive surgical procedures and excellent locoregional control, but most of these comparisons have been retrospective. Furthermore, it is unclear whether more extensive dissection actually leads to improved survival or whether these superior results are a function of more accurate staging (stage migration effect). Nonetheless, several recent studies have shown a positive association between the number of lymph nodes resected and overall survival. The question of optimal number of nodes examined in a specimen can be a moving target based on the pTNM stage of an individual patient and a function of whether or not preoperative chemoradiation was administered. Retrieval goals of 18 to 30 nodes per patient, regardless of treatment seem to be reasonable. To summarize the controversy, a good lymphadenectomy either improves overall survival or it improves the pathologic staging of the patient. It also happens to be a marker of surgical (and pathology) quality. In any case, so long as it does not increase the risk of the operation, performing regional lymphadenectomy in all of the at-risk nodal basins should be considered an essential part of the resection.

Regarding the technique of resection, prospective randomized studies in the United States and Western Europe have failed to show any significant difference in morbidity, mortality, or recurrence rates, or in the overall survival rate when comparing transhiatal esophagectomy with transthoracic or total thoracic esophagectomy. However, there is a survival trend favoring more radical transthoracic resections over a transhiatal approach, and local regional recurrence is known to be substantially higher after a transhiatal resection. In fact, subset analyses have shown that tumors located in the thoracic esophagus and cancers with positive but limited lymph node involvement benefit from a complete (at least two-field, including a thoracic dissection) esophagectomy compared to a transhiatal resection. The choice among surgical resection techniques should be individualized to the particular characteristics of the patient. The salient points that emerge from historical comparisons of these procedures is that a transhiatal resection has a tendency toward higher locoregional recurrence, but perhaps a lower respiratory complication incidence as it

does not require thoracotomy to complete. We personally reserve a transhiatal approach for extremes in age and stage, or for patients at high risk for thoracotomy.

Minimally invasive esophagectomy (MIE) is offered in many centers around the world. Patients with appropriate lesions have the option of undergoing esophageal resection with combined thoracoscopic and laparoscopic resection followed by a small neck incision with an esophagogastric anastomosis performed in the neck, or a minimally invasive Ivor Lewis resection. Complete laparoscopic (transhiatal) resections can also be accomplished, but again, this approach makes extensive en bloc resection of mediastinal lymph nodes difficult. Results on several hundred patients resected in this manner show no difference in survival, and a benefit in less blood loss, earlier return of bowel function, and a slightly shortened hospital stay. Disadvantages of this modality include a fairly steep learning curve, especially for surgeons with limited laparoscopic esophageal experience and prolonged anesthetic times (although very experienced surgeons can effectively resect the esophagus in a similar amount of time as open procedures). The key point in the discussion of MIE versus open resection is that MIE should not compromise the surgical/oncologic principles. If these goals can be maintained, then a less invasive option may be very attractive.

Reconstruction After Resection

The stomach, colon, and jejunum have all been successfully used as replacement conduits after esophagectomy. The stomach is used far more frequently because of the ease of mobilization, a hearty and redundant blood supply, limited perioperative morbidity, and the need to perform only one anastomosis.

The colon is a commonly used alternative replacement conduit. However, some surgeons prefer this conduit over the stomach in younger patients who are expected to have a prolonged survival because it provides a barrier between the stomach remnant and the residual esophagus, and this may prevent significant pharyngeal reflux and future esophageal metaplasia or dysplasia within the esophageal remnant. Either the right colon or the left colon can be used, but the segment of left and transverse colon that is supplied by the ascending branch of the left colic artery, arc of Riolan, and the marginal artery is generally a better size match to the esophagus and has more reliable arterial arcades. The colonic arterial

anatomy should be evaluated preoperatively by arteriography in any patient who is expected to have extensive limiting atherosclerosis or is suspected to have had a previous bowel resection. Otherwise, in patients with a naive abdomen, evaluation of the vasculature can take place in the operating theater. Another alternative is CT or MR angiography. Colonoscopy is necessary to rule out pathologic conditions, such as telangiectasia, polyposis, synchronous neoplasm, or extensive diverticulosis, which would preclude the use of the colon.

Jejunal reconstruction can be performed for lesions anywhere in the esophagus. Segmental free flaps transferred to the neck have been used successfully after resection of hypopharyngeal or upper cervical esophageal tumors. In this case, the mesenteric vessels are usually anastomosed to the external carotid artery and the internal jugular vein. Pedicled grafts are being used when segmental distal esophageal resection is performed for benign lesions requiring resection or confirmed short segment Barrett esophagus with HGD that is recalcitrant to efforts at endoscopic ablation. Pedicled jejunal flaps with proximal microvascular augmentation (long-segment supercharged jejunum) will allow for total esophageal replacement with the small bowel. This has some advantages over the colon in that small bowel has a good size match to the esophagus, is relatively free of intrinsic disease and does not require preparation before transfer.

Finally, musculocutaneous flaps are also frequently used for segmental cervical reconstruction and can be harvested from any of multiple areas with minimal physiologic or aesthetic effect.

Few prospective studies have been performed to evaluate the use of different replacement conduits, but evidence from several nonrandomized and small, randomized trials supports that overall survival is unchanged regardless of the technique used. A review performed by Urschel (2001) was unable to reach definitive results that would cause one technique to be favored over another. The basic principles are that the stomach has the most reliable blood supply and is associated with the lowest immediate postoperative morbidity. Cervical leaks from a colon interposition tend to be well tolerated and stricture rarely occurs. If strictures do occur, they are more easily dilated than those that occur with esophagogastric anastomoses. Graft loss can occur with any conduit in any position, cervical or intrathoracic. Pyloroplasty or pyloromyotomy may be required to avoid gastric stasis secondary to the division of the vagus nerves during

esophagectomy; however, with a trend toward using narrower conduits rather than whole stomach, this step remains somewhat controversial and several centers are reporting the omission of gastric drainage procedures without significant change in outcomes.

Results of Surgical Therapy

Perioperative mortality rates for transhiatal or transthoracic esophagectomies are now less than 3%, and realistic morbidity rates range from 35% to 65%. Overall survival rates after surgical resection correspond to the stage of the disease and vary drastically. The 5-year survival rates have been reported to be 60% to 95% for stage I, 30% to 60% for stage II, 5% to 30% for stage III, and 0% to 20% for stage IV (Fig. 8.1). Unfortunately, the vast majority (70%) of patients present with advanced stage III or IV disease at diagnosis.

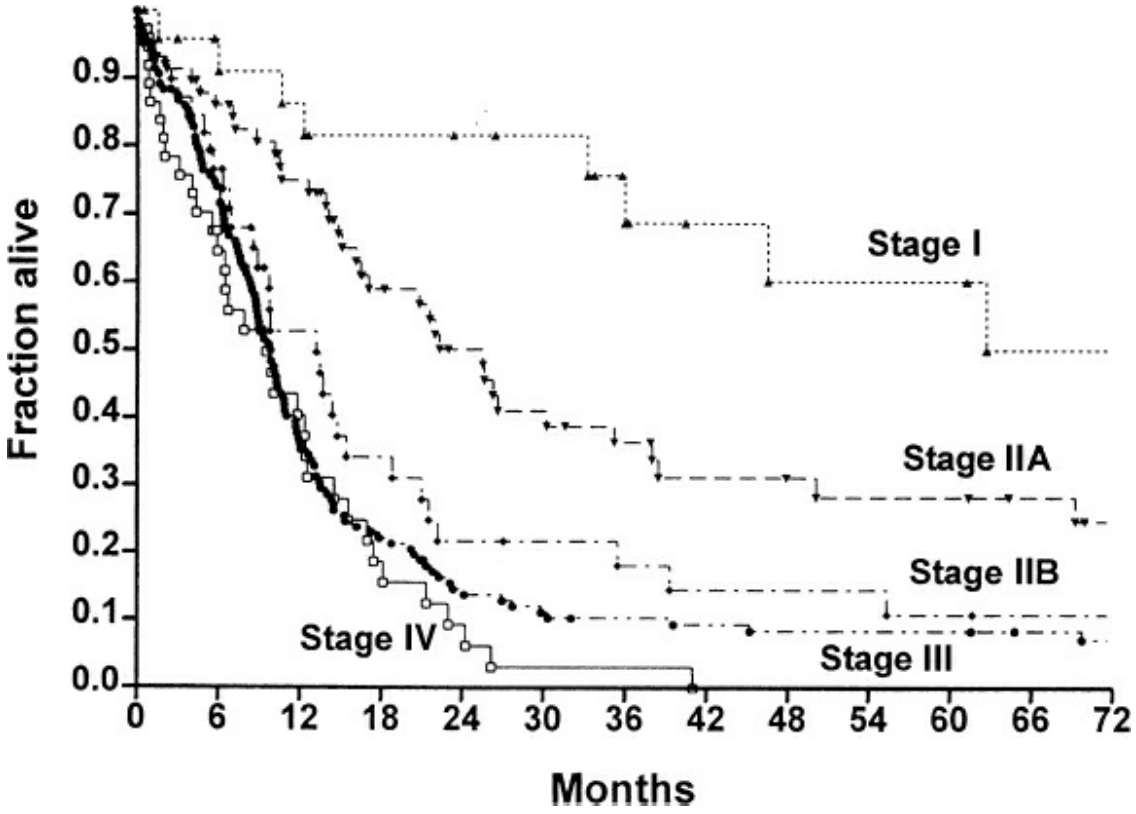

Figure 8.1 Survival curves for patients with esophageal cancer.

When examining the patterns of failure after surgical resection, one finds that most patients experience either distant metastasis or both locoregional and distant recurrence, while a small percentage experience solely a recurrence of localized disease. Novel treatment modalities

focusing on these patterns of failure have been explored to improve on the relatively poor prognosis afforded by surgery alone in most patients with esophageal carcinoma.

Adjuvant Therapy

Results of several randomized prospective trials on the use of adjuvant radiation therapy (45 to 56 Gy) after resection have been published. Traditionally clinicians would consider radiation therapy in patients with unexpected locally advanced disease, positive margins, or an R2 resection, although there is no scientific proof of benefit. Treatment-related toxicity can be severe. Overall, although reductions in local recurrences have been noted and specific subsets may benefit, no significant survival advantage has been found using adjuvant radiotherapy alone for esophageal carcinoma.

According to the results of prospective randomized trials, postoperative combination chemotherapy with various agents, including 5-fluorouracil (5-FU), cisplatin, mitomycin C, vindesine, and paclitaxel, have also not been proven to have a role in the treatment of completely resected lesions. Furthermore, adjuvant chemotherapy is generally poorly tolerated, and many patients fail to complete their treatment regimen. This treatment modality, therefore, is not recommended outside clinical trial settings.

Adjuvant chemoradiotherapy may benefit patients with esophageal carcinoma. This modality has the advantage of better patient selection because the pathologic stage will guide the decision to proceed to therapy. Patients with a high risk of recurrence (stage IIb and above) should be considered to selectively undergo treatment. In theory, chemoradiotherapy may increase survival by decreasing both distant and local disease. There is phase III evidence that has shown favorable results in a select group of patients with gastroesophageal junction adenocarcinomas treated with adjuvant chemoradiation, but compliance with treatment was not ideal. Patients take time to recover from esophagectomy and are often not physiologically prepared to handle additional postoperative toxicity in the form of treatment. Data on patients with squamous cancers, on the other hand, has been mixed. Most studies have not shown benefit from adjuvant chemoradiation after complete resection.

Neoadjuvant Therapy

Largely because of the difficulty administering adjuvant therapy to postesophagectomy patients and the disappointing results of trials with adjuvant chemotherapy or radiation monotherapy, researchers turned their attention toward the use of preoperative or neoadjuvant therapy. Preoperative radiation therapy has been investigated in several prospective randomized trials, and the results have been subjected to meta-analysis. Despite some initial responses, the results of these trials have shown marginal benefit in terms of overall survival rate. Preoperative radiation therapy alone is therefore not generally recommended, even in the setting of a clinical trial.

Results of phase II studies of induction chemotherapy were promising, but many small subsequent prospective randomized trials using multiple different drug combinations failed to show any advantage in overall or progression-free survival. This is despite the observation that neoadjuvant chemotherapy was capable of significant tumor response in the majority of patients. However, the net gain in survival was not significantly different from controls. Conjecture on the reasons for this are that toxicity and failure to receive all of the therapy, including an issue that the overall resection rate was lower in patients undergoing neoadjuvant therapy, abolished any potential therapy benefit. In contrast, the largest trial on induction chemotherapy involving more than 800 patients with esophageal carcinoma (squamous and adeno) performed in Europe (MRC Trial, 2002) did show a significant survival advantage over surgery alone. Furthermore, the long-term follow-up of the MRC trial continued to show a survival advantage in the treatment arm. Because complete response is a relatively rare event with preoperative chemotherapy, and tumor viability is a surrogate endpoint to survival, interest in chemotherapy as a neoadjuvant monotherapy has been mostly diverted to combined chemoradiotherapy.

Neoadjuvant chemoradiation therapy (CXRT) for esophageal carcinoma has been shown to be feasible and effective. Radiation to 50.4 Gy is given concurrently with a doublet of chemotherapy (fluorouracil and a platinum combination is currently the most common regimen) which is well tolerated without significantly increasing perioperative mortality (in experienced centers). Phase II trials reported excellent overall response rates (complete responses in 25% to 35%) and relatively decent compliance with therapy. Survival compared favorably to historical controls. The following decade of multiple small, prospective randomized trials lead to confusion over the potential benefit of preoperative CXRT.

Some trials showed benefit while others did not. Complicating the issue was the fact that the studies showing benefit had significant study design flaws. At this point, three randomized trials comparing preoperative CXRT to surgery alone have observed survival benefit with therapy. The Walsh trial, conducted at the University of Dublin with 113 patients with adenocarcinoma, evaluated neoadjuvant cisplatin plus 5-FU and 40 Gy of radiation with surgery alone. The investigators reported a 25% complete pathologic response rate, as well as a significant increase in median survival (16 vs. 11 months) and 3-year survival rate (32% vs. 6%) for the patients receiving the neoadjuvant treatment. Much of the debate over this study has focused on the poor survival in the surgery-only arm of 6% at 3 years, erratic preoperative clinical staging, and questions of miscalculations within the statistics. The CALGB trial (Tepper et al.) also showed a significant survival advantage with CXRT but the trial reached only 10% of its accrual goals and had a very poor outcome in the surgical arm, similar to the Walsh trial. Finally, the CROSS trial published in 2012 showed a significant improvement in survival with doublet chemotherapy cocktail given concurrently with 41 Gy of radiation. A positive finding in this study was that patients in the surgery-alone arm fared reasonably well, but not as well as with CXRT. Additionally, the R0 resection rate was better after preoperative therapy. There was limited toxicity in the trial, with similar perioperative morbidity and mortality in both arms of the trial. On the critical side, the study combined SCCA and adenocarcinoma. The differential hazard ratios indicate that the following variables: male sex, N0, SCCA, and good performance status really pushed the trial to significant differences in outcome. Despite the controversy in all of the randomized data, three separate meta-analyses have been published comparing neoadjuvant therapy to a surgery-alone arm. All favored the treatment arm, although squamous cancers and the Walsh trial may be adding a significant amount of weight to the calculated hazard ratios.

Definitive Chemoradiation Therapy

Although surgical resection remains the preferred therapy for esophageal cancer, definitive radiation therapy and chemoradiation therapy have been used in patients who opt out of, or who are not candidates for, surgical resection. Local control rates ranged between 40% and 75%, and median and 2-year survival rates ranged from 9 to 24 months and from 18% to 38%, respectively. Several prospective randomized trials have shown that

definitive chemoradiation therapy is superior to radiation therapy alone in the treatment of esophageal cancer. A trial published by Stahl et al. (2005) from Germany sought to evaluate the additional benefit of surgery in patients with SCCA after neoadjuvant chemoradiotherapy. The trial showed significantly improved locoregional control in the surgery arm compared with chemoradiotherapy alone and greater freedom from the use of palliative procedures after surgery. However, despite a local–regional recurrence rate approaching 60% in both the German and the French definitive chemoradiation trials (FFCD, Bedenne et al., 2007), neither trial was able to demonstrate a statistically significant difference in overall survival after surgery, largely due to the fact that these multicenter trials had a high perioperative mortality incidence, and both modalities failed to prevent death from distant disease.

Other Therapeutic Modalities

In certain parts of the world, particularly in areas where esophageal cancer is endemic, mass screening and advances in diagnostic techniques have led to the detection of increased numbers of superficial esophageal cancers. Studies from Japan and the United States have suggested that for lesions confined to the epithelium and lamina propria, lymphatic spread is rare. In some of these patients, EMR is a feasible option, although experience with this technique is still limited. Endoscopic ablative therapy using radiofrequency ablation, cryotherapy, and photodynamic therapy can be used for palliating large otherwise untreatable tumors, but in patients with superficial cancers and carcinoma in situ, these methods can also be curative. Although experience with these techniques is limited, investigators have reported tumor-free survival for several months after therapy, although recurrence rates after about 1 year can be significant. Similarly, photodynamic therapy has been used in nonsurgical candidates, and results of preliminary studies in patients with early-stage tumors have suggested that tumor-free survival can last several months and that complete remission is possible in some patients (at 2-year follow-up). However, long-term studies are still needed.

Palliation for Unresectable Tumors

Common indications for palliation in patients with advanced disease include dysphagia, presence of esophagorespiratory fistula, recurrent

bleeding, and prolongation of survival. Tumor debulking surgery has been performed, and although survival duration seems somewhat improved relative to that in patients who did not undergo resection, few randomized trials have been performed, and morbidity can be significant. Other options for palliation include (a) dilation, which is a safe and effective method to relieve dysphagia, although it usually requires multiple procedures; (b) stents, both rigid and expandable, which have become very popular in recent years for relieving dysphagia and for treating fistulas and bleeding; (c) laser therapy, which has been effective in relieving dysphagia from shorter strictures and those with intraluminal rather than infiltrative growth; (d) photodynamic therapy, which results in fewer perforations than do dilations or laser therapy and is tolerated better but requires more frequent sessions; (e) bipolar electrocautery and coagulation with tumor probes that use heat to destroy tumor cells and cause circumferential injury; and (f) brachytherapy, which delivers radioactive seeds intraluminally.

All of these techniques have advantages and disadvantages, and short-term success rates of 80% to 100% have been reported. If these treatment options fail, an endoscopic prosthesis can often be placed with good results. These techniques are not without complications, however, and ulceration, obstruction, dislocation, and aspiration have all been reported. Recently, improvements in definitive radiation therapy and chemotherapy have also provided excellent means for short-term palliation. With nonoperative treatment, however, long-term local control is still poor (40% locoregional failure). Which method to use therefore depends on the experience of the physician and the particular needs and condition of the patient.

Surveillance

A barium swallow study should be obtained in the first postoperative month as a baseline study. Asymptomatic patients can be assessed with yearly physical examinations and chest radiography. Any symptoms (e.g., pain, dysphagia, and weight loss) should be evaluated aggressively with CT scanning, barium studies, or endoscopy. Benign strictures at the anastomosis should be treated with dilation. Unfortunately, treatment options are limited for locoregional or distant recurrences. If radiation therapy was not given preoperatively or postoperatively, it can be used along with the previously mentioned nonoperative methods of palliation

(i.e., dilation, stenting, laser, photodynamic, or thermal resection).

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9 Primary Gastric Malignancies

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INTRODUCTION

Gastric cancer is a common solid organ malignancy and a leading cause of cancer-related death worldwide. The treatment of gastric cancer is evolving rapidly, as advances in both operative approaches and chemoradiation regimens develop. Gastric cancer is a malignancy that truly demands multidisciplinary collaboration between medical, radiation, and surgical oncologists. Ancillary services such as nutritional assessment and support and endoscopic support are also critical components to achieving successful outcomes for centers treating gastric cancer. The timing and interplay between systemic chemotherapy, operative resection, and radiation therapy are areas of intense study in an effort to improve survival outcomes. The treatment of advanced, incurable disease is a situation that requires thoughtful consideration of the patient's needs and goals. This chapter will cover these topics, mostly as they relate to gastric adenocarcinoma. Brief mention will be made of the treatment of other gastric malignancies, including gastric lymphoma and gastric neuroendocrine tumors (NETs). Gastrointestinal stromal tumors (GISTs) will be discussed in chapter 5.

EPIDEMIOLOGY, RISK FACTORS, AND GENETICS

Epidemiology

The incidence and public health burden of gastric adenocarcinoma varies greatly worldwide. The incidence in the United States has declined steadily over the last century. Whereas it was a leading cause of cancer-related deaths in the first half of the 20th century, responsible for 20% to 30% of all cancer-related deaths in the United States in the 1930s, currently it accounts for only about 2% of cancer-related deaths. Approximately 26,000 new cases of gastric adenocarcinoma and nearly

11,000 deaths are expected in the United States in 2016. In comparison, globally, gastric adenocarcinoma remains a significant public health burden. It is the fifth most common malignancy worldwide and the third leading cause of cancer death. There is a higher incidence in developing countries compared to developed countries. Similar to the United States, however, the incidence globally has declined over the last several decades. The highest incidence rates are in Japan and eastern Asia, followed by South America.

Incidences and death rates vary by race, gender, and ethnicity in the United States. Incidence rates are approximately twofold higher in non-Hispanic blacks and Asian/Pacific Islanders compared to non-Hispanic whites. Mortality rates are similarly approximately twice as high in non-Hispanic blacks and Asian/Pacific Islanders compared to non-Hispanic whites. Across all races and ethnicities, incidence and death rates are approximately twice as high in males compared to females.

Risk Factors

There is a complex interaction between environment and ethnicity contributing to differences in incidence rates of gastric cancer. In geographic terms, the highest rates of gastric cancer are seen in Japan and other eastern Asian countries, including China and Korea. Studies examining patterns of gastric cancer in ethnic migrant groups suggest that there are both environmental and ethnic factors involved. First-generation migrants from high-incidence to low-incidence countries have the same risk of gastric cancer as that of their native country. Subsequent generations acquire the risk rate of their new environment, indicating that the risk might not be entirely influenced by ethnicity but also by the environment.

Atrophic gastritis, intestinal metaplasia, dysplasia, and infection with *Helicobacter pylori* have been identified as important steps in the pathogenesis of gastric cancer. *H. pylori* plays a critical role in the development of gastric cancer. *H. pylori* is common in patients with distal (noncardia) cancer but not in patients with proximal cancer. A falling incidence of *H. pylori* infection and noncardia gastric cancers in developed countries coincides with increasing incidence rates of cardia and GEJ tumors. *H. pylori* infection is more prevalent in the populations of developing nations than in industrialized nations. *H. pylori* infection is disproportionately associated with intestinal-type gastric cancer, in which

the incidence of *H. pylori* infection is almost 90%, compared to 32% in diffuse type. The risk of adenocarcinoma is increased in patients with evidence of *H. pylori* antibodies and in patients with prolonged (>10 years) infection.

Diet is believed to play a major role in the pathogenesis of gastric adenocarcinoma and is likely an important factor in the geographic differences in gastric cancer incidence. Diets rich in salt, smoked or poorly preserved foods, nitrates, nitrites, and secondary amines are associated with an increase in gastric cancer. Prolonged exposure to this type of diet results in alterations in the gastric environment with the generation of carcinogenic *N*-nitroso compounds. Diets high in raw vegetables, fresh fruits, vitamin C, vitamin A, calcium, and antioxidants are associated with a decreased risk of gastric cancer.

Lifestyle factors are associated with an increased risk of gastric cancer in the United States. Occupational-associated increased risk may exist for metal workers, miners, and rubber workers, as well as for workers exposed to wood or asbestos dust. Obesity is associated with proximal gastric cancers. Cigarette smokers have a two to three times increased risk of proximal gastric cancer. Alcohol consumption has not been correlated with the development of gastric carcinoma.

Unlike colorectal adenocarcinoma, polyps are rarely precursor lesions of gastric adenocarcinoma. Hyperplastic polyps are the most common type of polyps found in the stomach. In general they are not associated with increased risk of malignancy when there is no dysplasia present. However, dysplasia can be present in some hyperplastic polyps. These lesions would have increased risk of subsequent malignancy. Risk factors for malignancy in hyperplastic polyps include size >1 cm and a pedunculated shape. Villous adenomas, though rare, are associated with increased risk of invasive cancer, both in the polyp itself and elsewhere in the stomach. Chronic atrophic gastritis and intestinal metaplasia are known precursor lesions for gastric adenocarcinoma and are also markers of increased risk in general. *H. pylori* is the most important risk factor for these precursor lesions, and the eradication of *H. pylori* is recommended when these lesions are discovered. The role of acid reduction by H_2 blockade or with proton pump inhibitors to reduce the risk of invasive malignancy when these precursor lesions are found is unclear.

Pernicious anemia is a risk factor for multiple types of gastric cancer. The presence of pernicious anemia in US elderly population was

associated with a 2-fold increased risk of noncardia gastric adenocarcinoma and 11-fold increased risk of gastric carcinoid. Operations for benign peptic ulcers also appear to be associated with an increased risk of gastric cancer. Adenocarcinoma in the gastric remnant may appear several decades after the index peptic ulcer operation and appears to increase over time. Finally, chronic, nonhealing gastric ulcers must be carefully evaluated endoscopically with multiple biopsies to determine if an underlying invasive malignant component is present. Epstein–Barr virus infection is associated with a specific form of gastric adenocarcinoma, one that is more prevalent in Hispanics and non-Hispanic whites compared to Asians, more often in the cardia and body, and more often diffuse type. All of these risk factors contribute a small marginal increase to the lifetime risk of gastric cancer. Even in the presence of these risk factors, the absolute lifetime risk may still be small.

Genetics

Most gastric carcinomas occur sporadically, however, 1% to 3% of them have an inherited familial component. Patients with germline mutations in p53 (Li–Fraumeni syndrome) and BRCA2 are at increased risk for developing gastric cancer and should be followed under close endoscopic surveillance. Gastric cancer can also develop as part of the hereditary nonpolyposis colon cancer syndrome, as well as part of the gastrointestinal polyposis syndromes, including familial adenomatous polyposis, MUTYH-associated adenomatous polyposis, juvenile polyposis syndrome, PTEN-associated hamartoma tumor syndrome (Cowden syndrome), and Peutz–Jeghers syndrome.

Germline mutations in the gene *CDH1* encoding the cell adhesion protein E-cadherin results in an autosomal-dominant predisposition to gastric carcinoma, known as hereditary diffuse gastric cancer. The cumulative risk of invasive gastric cancer in patients with the *CDH1* mutation is 70% in men and 56% in women. Endoscopic surveillance is not a reliable strategy to prevent invasive malignancy in these patients. The lesions are diffuse type and difficult to identify endoscopically. Prophylactic gastrectomy is offered to carriers of this mutation. The timing of the operation depends on the patient’s medical and social situation. In general, the operation is performed when the patient is young (in their 20s), or no later than 10 years prior to the earliest age of gastric cancer diagnosed in their family. Virtually all carriers of this mutation have

multiple foci of intramucosal adenocarcinoma in the resected specimen.

PATHOLOGY

The vast majority of gastric cancers are adenocarcinomas that arise almost exclusively from the mucus-producing rather than the acid-producing cells of the gastric mucosa. The remaining types of gastric cancer include lymphoma, carcinoid, leiomyosarcoma, GISTs, and adenosquamous and squamous cell carcinoma. Gastric tumors are classified according to their site in the proximal (cardia) and distal (noncardia) stomach. Proximal tumors in the cardia are staged as esophageal tumors in the latest edition of the *AJCC Staging Manual*. Although the incidence of distal gastric cancer is decreasing in the United States, the incidence of proximal gastric tumors continues to increase. Cancers of the gastric cardia currently account for nearly 50% of all cases of gastric adenocarcinoma. Gastric cardia tumors are five times more common in men than women, whereas noncardia gastric tumors are twice as common in men as in women. Nine percent of patients have tumor that involves the entire stomach; this is known as linitis plastica or “leather bottle” stomach, and the prognosis for these patients is dismal. In general, gastric tumors are more common on the lesser curve of the stomach than on the greater curve. In the United States, the incidence of synchronous gastric lesions is 2.2%, compared with an incidence of up to 10% in Japanese patients with pernicious anemia.

The most common classification scheme is a two-category system called the Lauren classification. According to the Lauren classification, there are two histologic types of gastric adenocarcinoma: intestinal and diffuse. The intestinal type is found in geographic regions where there is a high incidence of gastric cancer and is characterized pathologically by the tendency of malignant cells to form glands. These tumors are usually well to moderately differentiated and associated with metaplasia or chronic gastritis. They occur more commonly in males and older patients. These tumors tend to spread through the lymphatics and hematologically to distant organs, most often the liver. The diffuse type typically lacks organized gland formation, is usually poorly differentiated, and has many signet ring cells. If more than 50% of the tumor contains intracytoplasmic mucin, then it is designated as signet ring type. Diffuse-type tumors are more common in younger patients with no history of gastritis and spread transmurally and by lymphatic invasion. Diffuse-type tumors appear to be associated with obesity. Although the incidence of these tumors varies

little from country to country, their overall incidence appears to be increasing worldwide. The Lauren classification has its limitations, which include difficulty in assessing the classification on limited endoscopic biopsies and inability to classify patients who have had a significant response to preoperative therapy. An alternative classification scheme is used by the World Health Organization, which classifies gastric adenocarcinomas according to their histologic appearance, which includes tubular, mucinous, papillary, and signet ring cell types.

CLINICAL PRESENTATION

Gastric adenocarcinoma is insidious in onset, lacking outward signs of early disease. Patients and physicians often ignore the vague epigastric discomfort that in hindsight was present for months prior to diagnosis. The most frequent presenting symptoms are weight loss, pain, vomiting, and anorexia. Dysphagia is more commonly associated with tumors of the cardia or gastroesophageal junction (GEJ). Tumors in the antrum may cause symptoms of gastric outlet obstruction; this is an ominous sign of advanced disease. Although rare, large tumors that directly invade the transverse colon may present with colonic obstruction. Physical examination will reveal a palpable mass in up to 30% of patients. Chronic anemia is also a common finding that prompts endoscopic evaluation that reveals an otherwise occult gastric cancer.

Approximately 40% of patients in the National Cancer Database with gastric adenocarcinoma have stage IV metastatic disease at the time of presentation. Stage at presentation may vary with race and ethnicity. Physical examination findings that suggest metastatic disease include a palpable supraclavicular lymph node (Virchow node), a mass palpable on rectal examination (Blumer shelf), a palpable periumbilical mass (Sister Mary Joseph node), or the presence of ascites or jaundice. Intestinal-type gastric cancer most commonly metastasizes to the liver, while peritoneal metastases are the most common site of metastases for diffuse type.

ASSESSMENT

The National Comprehensive Cancer Network (NCCN) has developed consensus guidelines for the clinical evaluation and staging of patients suspected of having gastric adenocarcinoma. The recommended initial evaluation includes complete history and physical examination and

laboratory studies. In addition to routine laboratory studies like complete blood count and chemistry panels, a carcinoma embryonic antigen (CEA) level may be obtained at time of diagnosis. CEA may only be elevated in approximately 30% of patients with gastric carcinoma, but when elevated it is a useful marker to follow for treatment response and to monitor for recurrence. Nutrition labs may be helpful to identify malnutrition and to guide decision making regarding operative timing.

Chest, abdominal, and pelvic computed tomography (CT) scans are performed early in the overall staging of patients with newly diagnosed gastric cancer. This allows early identification of solid organ metastases, malignant ascites, or possibly large peritoneal metastases. The major limitations of CT as a staging tool are in the evaluation of early gastric tumors and small (<5 mm) metastases on peritoneal surfaces or in the liver. The use of fluorodeoxyglucose (2-deoxy-2-[^{18}F]fluoro-D-glucose) positron emission tomography (FDG-PET) may improve the detection of otherwise occult metastases in patients with locally advanced (T3, T4, or node positive) disease and can be considered as part of the staging workup.

Endoscopic evaluation is essential for the staging of gastric cancer. Esophagogastroduodenoscopy allows for direct anatomic localization of the tumor and sampling of tissue for diagnostic purposes. Endoscopic ultrasound (EUS) is a useful tool to predict the T classification of the tumor and identify perigastric lymph nodes that are suspicious for metastases. An added benefit of EUS is the ability to perform fine-needle aspiration biopsy of suspicious lymph nodes to confirm node-positive disease. The addition of EUS to cross-sectional CT imaging improves the accuracy of both T and N classification.

Staging laparoscopy is also a critical part of the initial assessment and staging of patients with newly diagnosed gastric adenocarcinoma. This minimally invasive procedure serves two purposes: (1) to identify small (<5 mm) peritoneal metastases often missed by CT imaging, and (2) to obtain peritoneal washings for cytology to identify microscopic peritoneal metastatic disease. Our preference is to perform this procedure separately as an outpatient as part of the patient's initial staging workup, rather than immediately prior to a planned definitive resection. The intent is to identify metastatic peritoneal disease, therefore nodal biopsy is not routinely performed. In our experience at MD Anderson, routine laparoscopy performed in patients with gastroesophageal or gastric adenocarcinoma identified radiographically occult macroscopic peritoneal

metastases in 21% of patients, positive cytology in lavage specimens in another 13% of patients, and unexpected clinically relevant findings (such as liver metastases or cirrhosis) in another 6% of patients. The total yield of diagnostic laparoscopy in these patients was 36%. Patients with microscopically positive peritoneal cytology findings have a prognosis similar to that of patients with macroscopic visceral or peritoneal disease. A repeat diagnostic laparoscopy prior to planned resection in patients with locally advanced disease after neoadjuvant treatment can also be considered and may identify radiographically occult metastatic disease in a minority of patients.

STAGING

The American Joint Committee on Cancer (AJCC) staging guidelines, based on the tumor (T), node (N), and metastasis (M) classification is the most commonly used system to stage gastric adenocarcinoma. The Japanese classification historically refers to the extent of lymph node dissection by D classification. The Japanese classification is harmonized with the AJCC TNM system, with more detail regarding the preoperative macroscopic appearance of the lesions and the designation of the nodal stations involved.

American Joint Committee on Cancer Staging System

The eighth edition of the *AJCC Staging Manual* published in 2016 preserved most of the significant updates made to the seventh edition in 2010. The eighth edition updated the distinction between gastric and esophageal adenocarcinoma of the GEJ. Tumors at the GEJ with the epicenter of the tumor greater than 2 cm into the proximal stomach are staged as gastric cancer; those with an epicenter less than 2 cm into the proximal stomach are staged as esophageal cancers. Staging of esophageal tumors will be discussed in Chapter 8. The staging system relies on the classic tumor (T), node (N), and metastasis (M) classification. The updated eighth edition defines clinical, pathologic, and postneoadjuvant therapy stage groupings. The system is designed to stratify patients according to their overall survival. Stages are grouped to identify survival differences, thus there is a mix of T and N classifications in each stage designation (Table 9.1).

When comparing studies from different time periods, care must be paid

to changes in staging definitions. The T classification regarding depth of invasion was aligned with other gastrointestinal tract malignancies, such as the esophagus and small and large bowel. The modification of T stage in the seventh edition from previous editions include: tumor penetrates subserosal tissue (previously T2b, currently T3), serosa (previously T3, currently T4a), and adjacent structures (previously T4, currently T4b). These modifications are preserved in the eighth edition.

TABLE 9.1 TNM Classification of Carcinoma of the Stomach

Definition of Primary Tumor (T)

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades muscularis propria[a]
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures[b,c]
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures[b,c]
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs

Definition of Regional Lymph Node (N)

N Category	N Criteria
Nx	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 or 2 regional lymph nodes
N2	Metastasis in 3–6 lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Clinical (cTNM)

When T is…	And N is…	And M is…	Then the Stage Group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB

Pathologic (pTNM)

When T is…	And N is…	And M is…	Then the Stage Group is…
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T3	N0	M0	IIA
T1	N3a	M0	IIB
T2	N2	M0	IIB
T3	N1	M0	IIB
T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC
T4b	N3a	M0	IIIC
T4b	N3b	M0	IIIC
Any T	Any N	M1	IV

Postneoadjuvant Therapy (ypTNM)

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III

Postneoadjuvant Therapy (ypTNM)

When T is…	And N is…	And M is…	Then the Stage Group is…
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
Any T	Any N	M1	IV

[a]A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.
[b]The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
[c]Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.
Note: A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.
Adapted from Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
Used with permission of the American Joint Committee on Cancer (AJCC). *The Original Source For This Material is the AJCC Cancer Staging Manual*. 8th ed. Chicago, Illinois: Springer Science and Business Media LLC; 2017. www.springer.com.

The nodal classification in the eighth edition is the same as the seventh edition. The evaluation of the lymph nodes and the extent of lymph node resection have always been contentious issues in gastric cancer. The AJCC staging guidelines make no recommendations as far as extent of lymph node dissection required for accurate staging, only suggesting that at least 16 regional lymph nodes be removed and assessed pathologically. A pN0 designation can be assigned based on the actual number of lymph nodes evaluated microscopically.

The presence of metastatic disease is simply designated M1 without subclassification. Metastases to nonregional lymph node groups, including the retropancreatic, para-aortic, portal, retroperitoneal, or mesenteric groups, is considered M1 disease. Microscopically positive peritoneal cytology, in addition to frankly macroscopic peritoneal disease, is considered M1 disease.

Japanese Classification

Since 1962 when the first version of the Japanese Classification of Gastric Cancer was published, frequent modifications have been applied up to the current 14th version. The Japanese Classification not only defines

pathologic staging, but also describes all aspects of preoperative staging, intraoperative findings, how to handle resected specimens, rules of treatment effect on pathology, and detailed histologic classifications. There are also a series of Japanese Treatment Guidelines of Gastric Cancer, which summarize current consensus of stage-specific treatment strategies; currently it is on its fourth edition. The greatest advantage of the detailed Japanese classification is the standardization of the description of specific tumor status, which creates a standard format used by Japanese surgeons in each case. The disadvantages include its complexity which limits its broader acceptance and the frequent updates which make it difficult to compare results to historical literature. Efforts have been made to correspond to the AJCC staging system. The pathologic staging and grouping are now essentially identical to those of AJCC in the current version. N stage was previously defined by location of involved lymph nodes (stations) but is now defined by the number of involved lymph nodes in accordance with AJCC convention. However, GEJ tumors in the Japanese classification are not staged as esophageal cancers, therefore Siewert type 3 tumors are classified as gastric cancers in the Japanese classification. The current interest in Japan is to create a new classification for Siewert type 2 tumors, and a prospective study is underway to define the optimal surgical approach (right thoracotomy vs. transhiatal approach and examining the extent of lymph node dissection) for these tumors in Japan.

OPERATIVE TREATMENT

Operative resection offers the only significant potential for cure of gastric cancer. Preoperative staging should demonstrate the extent of disease, define the patient's prognosis, and permit treatment planning. The type of surgery is then dependent upon tumor depth, growth pattern, and tumor location. Early gastric cancer confined to the mucosa can be treated endoscopically with endoscopic mucosal resection (EMR). All other surgical resections are based on the location of the tumor and potential lymph node metastases, with the intent of microscopically negative surgical margins and clearance of the at risk lymph node groups.

Endoscopic Mucosal Resection

Gastric adenocarcinoma confined to the mucosa (T1a lesions) has a very

low rate of lymph node metastases, on the order of 0% to 5%. As such, if complete resection of these lesions is possibly via an endoscopic approach, acceptable locoregional disease control can be achieved with minimal comorbidities. EMR has very well-defined indications proposed by the Japanese Gastroenterological Endoscopy Society and the Japanese Gastric Cancer Association. The "absolute" indication for EMR is a well-differentiated tumor less than 2 cm in diameter confined to the mucosa without ulceration (T1a lesion). The expanded indications include nonulcerated, well-differentiated lesions greater than 2 cm in diameter; ulcerated, well-differentiated lesions less than 2 cm in diameter; and undifferentiated, nonulcerated T1a lesions less than 2 cm in diameter. When EMR is performed for lesions meeting the strict criteria of well-differentiated tumors without ulceration less than 2 cm in size confined to the mucosa, survival outcomes are excellent and similar to operative resection, on the order of 95% 5-year overall survival. Local recurrence rates are higher (approximately 6% vs. 1%), but most of these recurrences can be managed with repeat EMR. However, reports have described the use of expanded criteria such as resection of larger tumors, tumors with submucosal invasion, and for patients whose comorbidities preclude standard treatment with gastrectomy. Local recurrence rates are higher in these groups, but most studies report similar overall survival and long-term disease control with repeat EMR.

While the advantages and outcomes of EMR for early T1a gastric cancer are attractive, they must be considered in the appropriate clinical context. The reported experience is mostly from eastern Asia, where intense surveillance programs are in place and the incidence of early T1a gastric cancer is high. As such, experience with this complicated endoscopic technique is very high in these countries. Gastric cancer is rarely diagnosed at such an early stage in Western countries lacking dedicated surveillance programs. The approach remains an option for treatment in very early-stage gastric cancer, but the appropriate endoscopic expertise and commitment to long-term follow-up are necessary.

Extent of Resection

Tumor involving the GEJ with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancers. A margin-negative resection is the goal for treatment of these tumors. The operation to achieve complete resection may require an esophagogastrectomy, subtotal

esophagectomy with resection of the proximal stomach, or total gastrectomy with resection of the GEJ and distal esophagus, further described below. The approach can be abdominal, abdominothoracic, transhiatal, or transthoracic, via either an open or minimally invasive technique. Tumors at the GEJ and proximal stomach are treated via a multiteam approach at the MD Anderson Cancer Center. Siewert type I lesions that are associated with Barrett esophagus or that are true esophageal cancers descending into the GEJ are typically treated with an esophagectomy. Siewert type II lesions lying within 2 cm of the squamocolumnar junction at the level of the cardia or type III lesions in the subcardia region of the stomach are usually treated with a total gastrectomy, with resection of the distal esophagus only to the extent needed to achieve negative margins. This is performed with input from both the thoracic and surgical oncology teams, usually via an open transabdominal approach. We favor this approach so that a D2 lymph node dissection including the greater curvature lymph nodes can be performed in these patients. We recently reported that extended (D1+D2) lymph node dissection, including celiac and hepatic artery lymph nodes, was associated with improved survival in patients with GEJ tumors who underwent resection after neoadjuvant treatment. We do not in general perform proximal subtotal gastrectomies for these lesions in order to avoid alkaline reflux esophagitis.

Tumors located in the body and antrum make up the remaining 65% to 70% of gastric cancers. The decision to make is whether to perform a distal, subtotal, or total gastrectomy in these patients. As long as a margin-negative resection is performed, survival is equivalent among these operations. Quality of life and long-term nutrition status appears to be better in subtotal versus total gastrectomy. In these patients, we favor whatever extent of resection is needed to achieve a gross 5 cm margin. An adequate remnant proximal gastric pouch needs to be present to consider a subtotal gastrectomy. We do not perform a proximal subtotal gastrectomy with an esophagogastrostomy in more proximal body tumors, as mentioned above.

Lymphadenectomy

The extent of lymphadenectomy has been a much debated topic in gastric cancer treatment over the last several decades. Japanese surgeons have espoused radical lymphadenectomy and meticulous pathologic analysis,

with low perioperative morbidity and mortality. Western studies attempting to replicate these findings initially demonstrated alarmingly high rates of perioperative morbidity and mortality without survival benefit in extended lymphadenectomy. More recent data have supported more extensive lymphadenectomy for advanced disease, as long as it can be performed by experience surgeons with good outcomes.

The Japanese definition of D1 or D2 lymph node dissection is complicated even after recent simplification. The extent of D1/D2 lymph node dissection changes based on the extent of gastrectomy, and D3 is no longer defined. An important update of the D1/D2 classification in the current Japanese classification is that the left gastric artery lymph nodes (#7) should be included in a D1 lymph node dissection in addition to perigastric lymph nodes, regardless of the procedure type or tumor location. The right paracardial lymph nodes (#1) are also included in a D1 lymph node dissection in any tumor location or procedure type, whereas the left paracardial lymph nodes (#2) and splenic hilum nodes (#10) are not included in either a D1 or D2 dissection for distal tumors. These lymph nodes should not be dissected in antral or distal body tumors that can be resected with distal gastrectomy. The description in the NCCN guidelines defining D1/D2 lymph nodes is simple: N1 lymph nodes are defined as the perigastric lymph nodes in stations #1, 3, 5 (lesser curvature) and stations #2, 4, 6 (greater curvature), and N2 lymph nodes are defined as left gastric (#7), common hepatic artery (#8), celiac artery (#9), splenic artery (#11), and splenic hilum lymph nodes (#10) (Fig. 9.1). A lymph node dissection is classified as D0, D1, or D2; D0 refers to an incomplete resection of N1, D1 denotes a complete resection of N1, and D2 involves a complete removal of N1 and N2 lymph node stations. The extended D3 lymph node dissection, while it is no longer defined as such, includes further extent of lymph nodes such as para-aortic (#16) and retropancreatic (#13) lymph nodes.

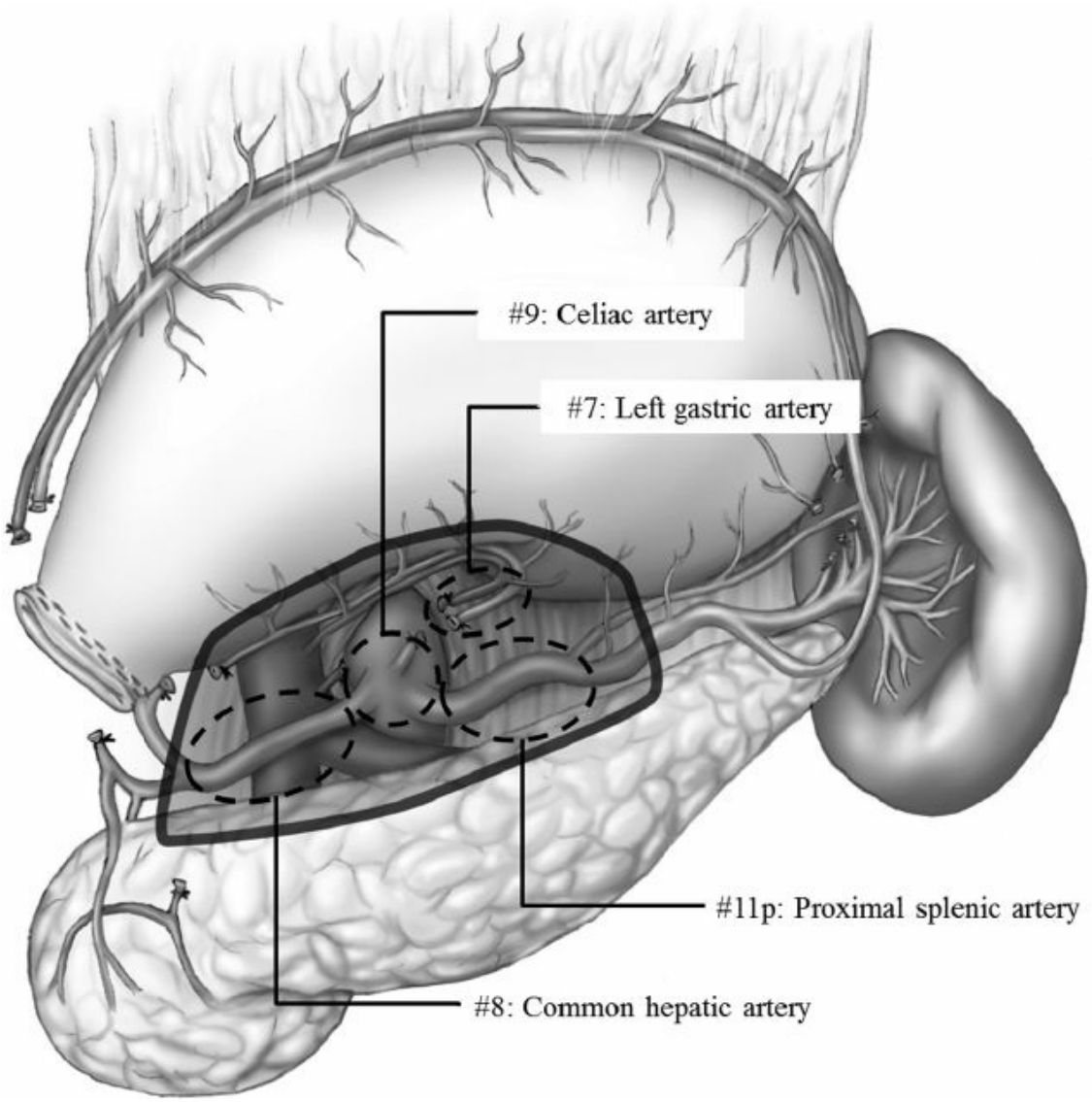

Figure 9.1 Lymph node stations for D2 lymph node dissection. (With permission from Paul F. Mansfield, MD.)

The relevant clinical trials examining D1, D2, and D3 lymphadenectomies are summarized in Table 9.2. The Dutch and UK trials initially reported high perioperative morbidity, high pancreatectomy and splenectomy rates, and high perioperative mortality, without any survival benefit for D2 versus D1 lymphadenectomy. Longer-term follow-up in the Dutch trial reported a statistically significant difference in overall survival, favoring D2 (15-year survival 29% vs. 21%). The Italian study, with strict quality control measures regarding definition of D1 and D2 dissections and the experience of the participating surgeons, reported much lower perioperative morbidity and mortality rates, reassuring the medical community that experienced surgeons could perform extended lymphadenectomy for gastric cancer safely. The Italian data also suggested

a survival benefit in subgroups with advanced disease (T2–4 tumors with positive lymph nodes). The Japanese Clinical Oncology Group Study 9501 reported excellent perioperative outcomes for D2 and D3 lymphadenectomies, without long-term survival benefit from the addition of a D3 dissection of the para-aortic lymph nodes.

The interpretation and implementation of these trial findings can be complicated. A limited D1 lymphadenectomy may be sufficient for early-stage gastric cancer, particularly in low-volume centers that may have higher complication rates. A more extensive D2 lymphadenectomy may be performed in the hands of experienced gastric surgeons who can do so with limited morbidity and mortality. The additional resection of para-aortic lymph nodes is not necessary to improve locoregional disease control or survival. At MD Anderson, our approach is a D2 lymphadenectomy, with emphasis on splenic preservation.

TABLE 9.2 Summary of Clinical Trials Comparing Extent of Lymph Node Dissection in Gastric Cancer

Author, Trial name, journal, year	Comparison	Perioperative Mortality	Morbidity	5 year Survival	Comments
Cuschieri, MRC Trial, Br J Cancer, 1999	D1 vs D2	6.5 vs 13%	28 vs 46%	35 vs 33%	very high perioperative mortality, high rates of pancreatectomy and splenectomy in D2 group associated with morbidity and mortality
Bonenkamp, Dutch Trial, NEJM, 1999 (*Songun, Lancet Oncol, 2010)	D1 vs D2	4 vs 10%	25 vs 43%	45 vs 47% *15 yr survival showed difference (21 vs 29%)	Incomplete lymph node dissection in 50% of D2 group, high rate of splenectomy/ pancreatectomy
Sano, JCOG 9501, J Clin Oncol, 2004	D2 vs D3	0.8 vs 0.8%	21 vs 28%	69 vs 70%	D3 – para-aortic lymph node dissection. Established that D2 could be performed with acceptable mortality/morbidity
Wu, Taipei trial, Br J Surg, 2004	D1 vs D2 + retropancreas LN	Not reported	Not reported	61 vs 54%	D3: D2 + retropancreatic lymph nodes.
Degiuli, Italian Gastric Cancer Study Group trial, Eur J of Surg Onc, 2004	D1 vs D2	3.0 vs 2.2%	12 vs 18%	67 vs 64%	Survival benefit for D2 in patients with T2–4 and N+ disease (59 vs 38%)

Splenectomy and En Bloc Multivisceral Resection

Splenectomy was once considered a part of D2 lymph node dissection in proximal gastric adenocarcinoma, however it is associated with increased morbidity and mortality. It is of paramount importance not to perform splenectomy with a distal gastrectomy, as the loss of the short gastric vessels can make the remnant stomach ischemic and increase the risks of complications. Most recently, the Japanese JCOG 0110 trial failed to a show survival benefit with splenectomy (and associated lymph node dissection of station #10) in patients with proximal gastric adenocarcinoma

not invading the greater curvature. It is still controversial whether a splenectomy should be performed (or station #10 lymphadenectomy) in tumors located at the proximal greater curvature, but based on currently available evidence, the spleen should be preserved unless directly involved. At MD Anderson, splenectomy is not performed unless the tumor adheres to or invades the spleen or its vascular supply.

Locally advanced tumors which invade adjacent structures are classified as T4b lesions. Resection of the involved organs in an effort to achieve negative R0 margins is acceptable if the patient can tolerate such an extensive operation. Lymph node metastases are common with locally invasive disease; they are present on the order of 60% to 90%. Perioperative morbidity increases with the extent of resection, with the highest complications being associated with concomitant pancreatectomy, although perioperative mortality is similar in patients who do and do not undergo multivisceral resections. If the patient is physically fit to undergo an extensive operation, has no evidence of metastatic disease, and an R0 resection is expected, we perform a multivisceral resection in locally advanced disease.

OPERATIVE TECHNIQUE

Staging Laparoscopy and Enteral Access

Diagnostic laparoscopy is performed in newly diagnosed patients without radiographic evidence of systemic or peritoneal metastases. The procedure is usually performed as an outpatient and a vascular port is also placed in anticipation of systemic chemotherapy. Either a closed optical trochar or open technique can be used to obtain laparoscopic access. The stomach, peritoneal lining, and the rest of the visceral organs are visually inspected in a systematic fashion. Any suspicious lesions are biopsied and sent for permanent pathologic analysis. One liter of normal saline is instilled into the right and left upper quadrants, then evacuated and collected for cytologic analysis.

If the patient has evidence of malnutrition, based on nutrition labs or precipitous weight loss, a poor performance status that is expected to decline during systemic chemotherapy treatments, or evidence of near complete or complete gastric outlet obstruction prohibiting adequate oral intake, a jejunostomy feeding tube is placed at the time of staging laparoscopy. A location at least 20 cm past the ligament of Treitz is chosen

at a point that easily reaches the abdominal wall. When a feeding tube is placed, the patient is admitted to the hospital while tube feeds are initiated and patient education is performed.

Total Gastrectomy

Our approach for a total gastrectomy begins with an upper midline incision that extends to or below the umbilicus (Fig. 9.2). The greater omentum is separated from the transverse colon up to and including the short gastric vessels (Fig. 9.3). While the perigastric lymph nodes in the greater omentum are resected en bloc, the more inferior portion of the omentum is preserved to form an omental pedicle flap. Dissection around the GEJ is performed, starting at the right crus then progressing over to the left crus anterior to the esophagus. The GEJ is encircled with a Penrose drain, mobilizing 7 to 8 cm of the distal esophagus to ensure an adequate proximal margin. The vagus nerves may be divided to provide additional mobilization. The right gastroepiploic vessels are ligated at their origin, and the subpyloric nodes are resected with the specimen. The first portion of the duodenum is mobilized and divided 2 cm distal to the pylorus with a stapling device (Fig. 9.4). The gastrohepatic ligament is opened, and the left gastric artery is ligated at its origin. A replaced or accessory left hepatic artery may originate from the left gastric artery and reside in the gastrohepatic ligament and should be preserved. A vascular clamp is placed across the esophagus, then the esophagus is divided either sharply or with cautery 2 to 3 cm proximal to the GEJ, and the specimen is passed off the field for frozen section evaluation of the margins (Fig. 9.5). Full-thickness stay sutures are placed to prevent the esophageal mucosa from retracting proximally. The hepatic, celiac, and splenic lymph node packets are then dissected and passed off separately to complete the D2 lymphadenectomy. If the tumor adheres to the spleen, pancreas, liver, diaphragm, colon, or mesocolon, the involved organ or organs are removed en bloc.

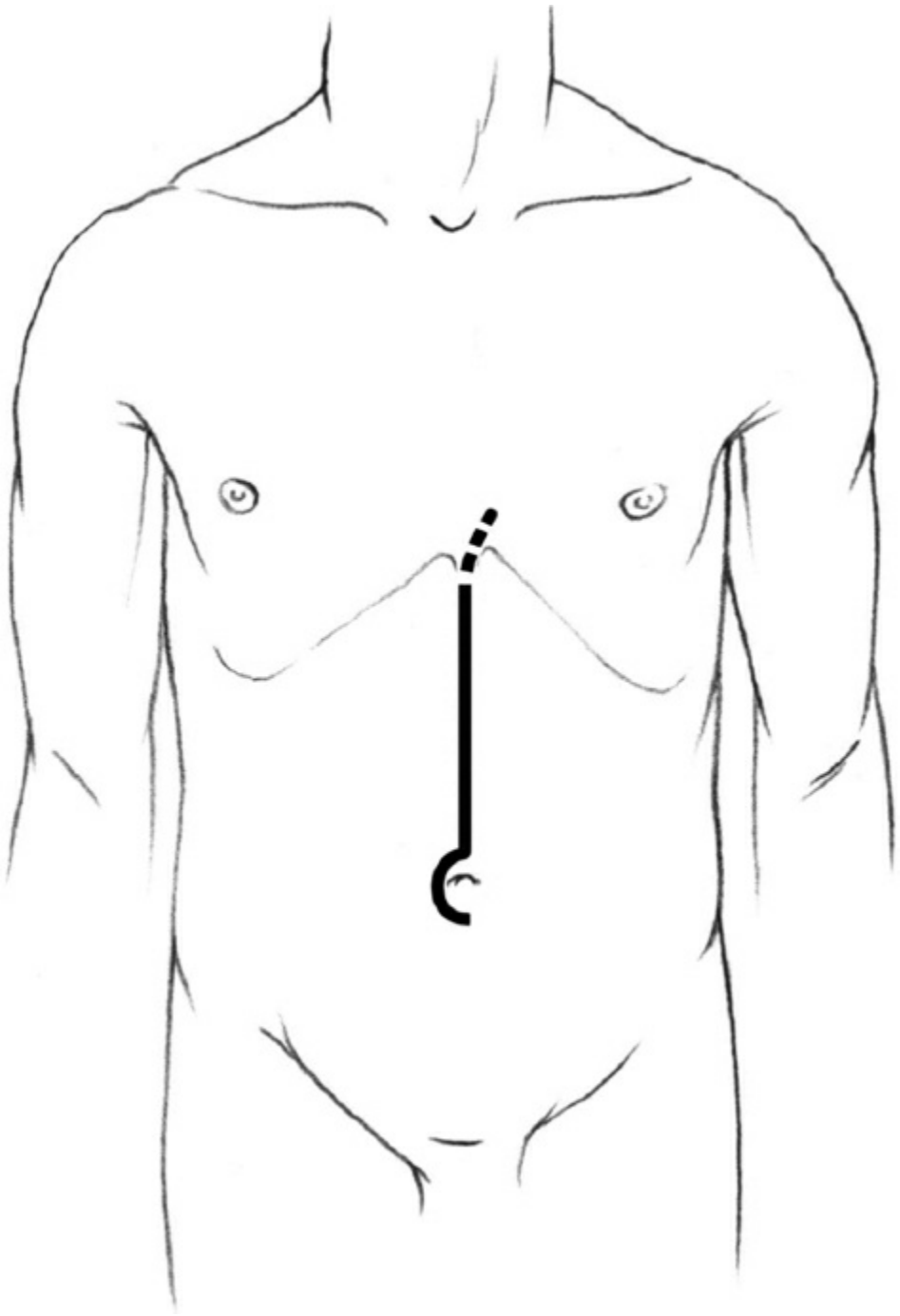

Figure 9.2 Upper midline incision for total gastrectomy. (With permission from Paul F. Mansfield, MD.)

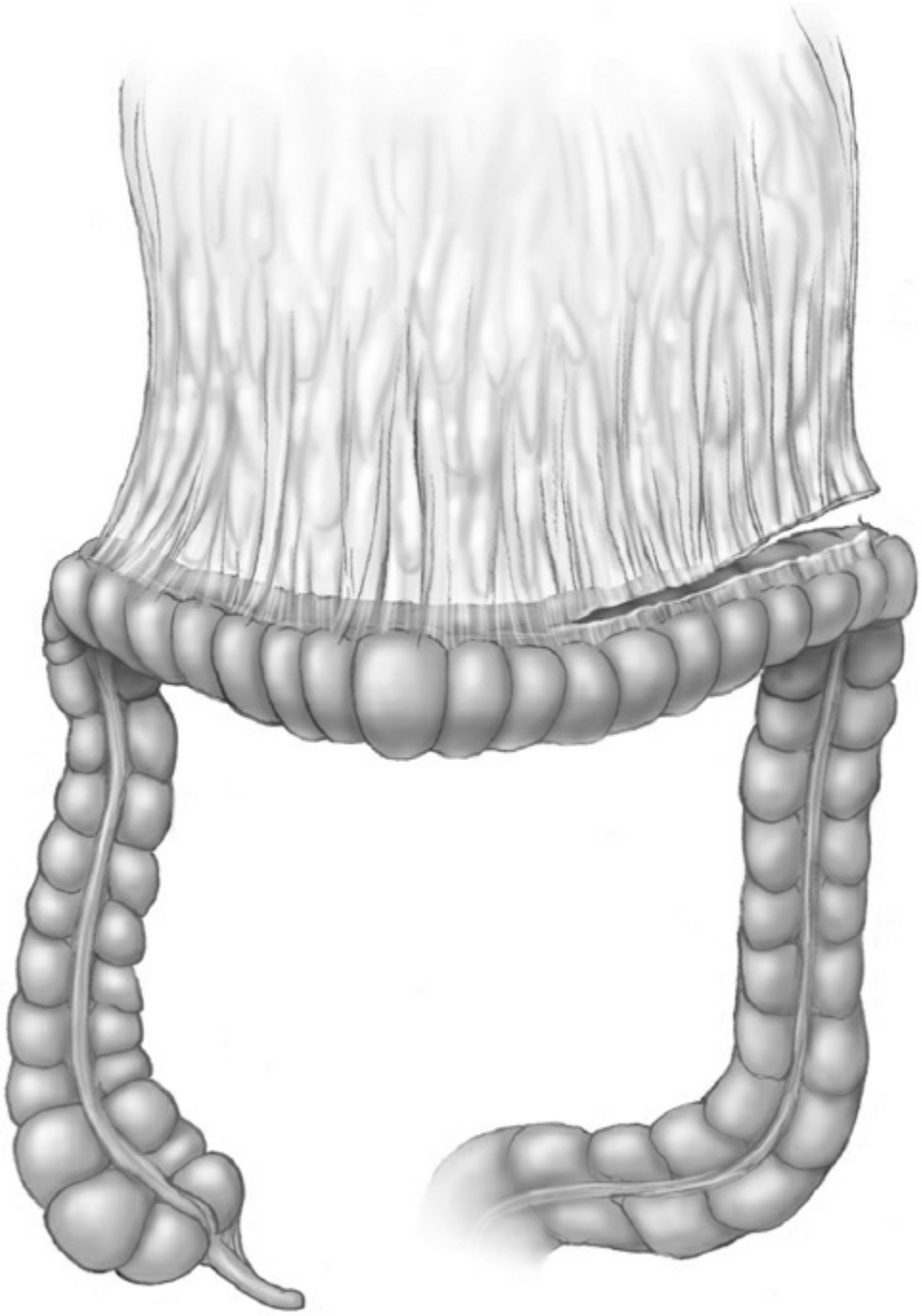

Figure 9.3 Mobilization of the omentum off of the transverse colon. (With permission from Paul F. Mansfield, MD.)

The most frequent reconstruction used is a Roux-en-Y anastomosis (Fig. 9.6). If a significant portion of the distal esophagus is resected, a left thoracoabdominal or right thoracotomy incision (Ivor Lewis approach) may be necessary. A 60-cm Roux limb is created and passed in a retrocolic fashion. The enteroenterostomy is performed. A hand-sewn single layer esophagojejunostomy is performed with interrupted sutures. The previously preserved omentum is wrapped around the anastomosis. No

drain is placed. A feeding jejunostomy tube is placed for postoperative nutritional support.

Subtotal Gastrectomy

The mobilization for subtotal gastrectomy is identical to that for total gastrectomy described in the preceding section, except that the short gastric vessels are preserved and only approximately 75% to 80% of the distal stomach is resected. A gross 5-cm margin is obtained proximal to the tumor. The small pouch of stomach that remains is supplied by the remaining short gastric vessels and the posterior gastric artery arising from the splenic artery. We often use Roux-en-Y reconstruction after subtotal gastrectomy, although a loop gastrojejunostomy (Billroth II) or less frequently a gastroduodenostomy (Billroth I) may be employed.

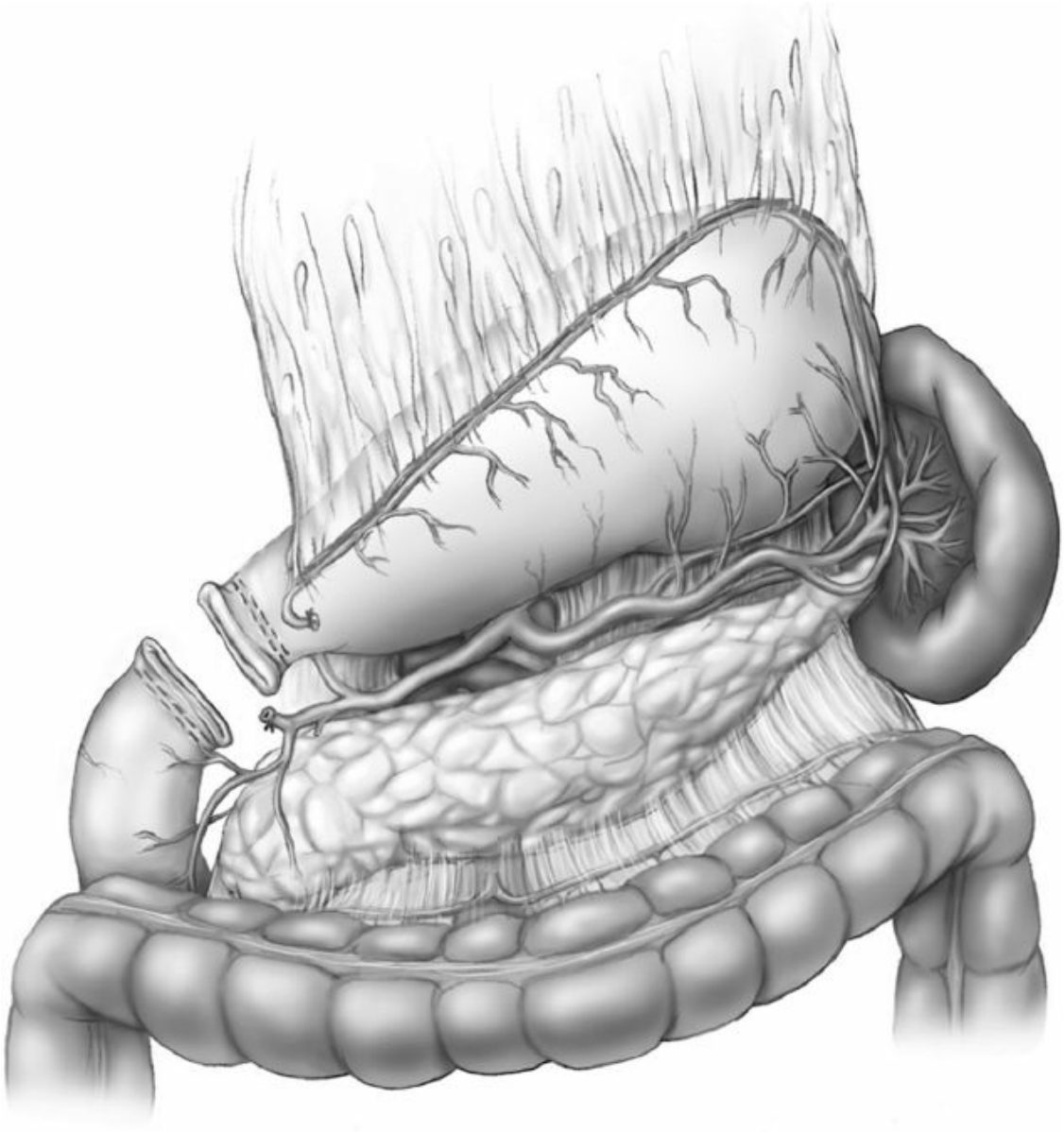

Figure 9.4 Division of the duodenum for total gastrectomy, 2 cm distal to the pylorus. (With permission from Paul F. Mansfield, MD.)

Laparoscopic Resection

Data continue to emerge that laparoscopic resection for gastric cancer is safe and oncologically sound. The technique was first attempted in distal gastrectomies for early gastric cancer, with promising results regarding patient reported outcomes. The KLASS-01 trial randomized 1,416 patients with clinical stage I (T1N0, T1N1, or T2aN0) gastric adenocarcinoma to either laparoscopic-assisted or open distal gastrectomy. Short-term results demonstrated no significant difference in perioperative morbidity and mortality; these results have been confirmed with longer follow-up.

Initially, studies focused on early gastric cancer. Now data are accumulating regarding the safety of minimally invasive approaches in advanced gastric cancers. Several meta-analyses have reported short-term outcomes that favor laparoscopic over open approaches in advanced gastric cancer. Early results from the KLASS-01 trial, a trial examining laparoscopic versus open distal gastrectomy with D2 lymphadenectomy for patients with advanced (T2–4aN0–3) gastric adenocarcinoma, report no differences in perioperative morbidity or mortality.

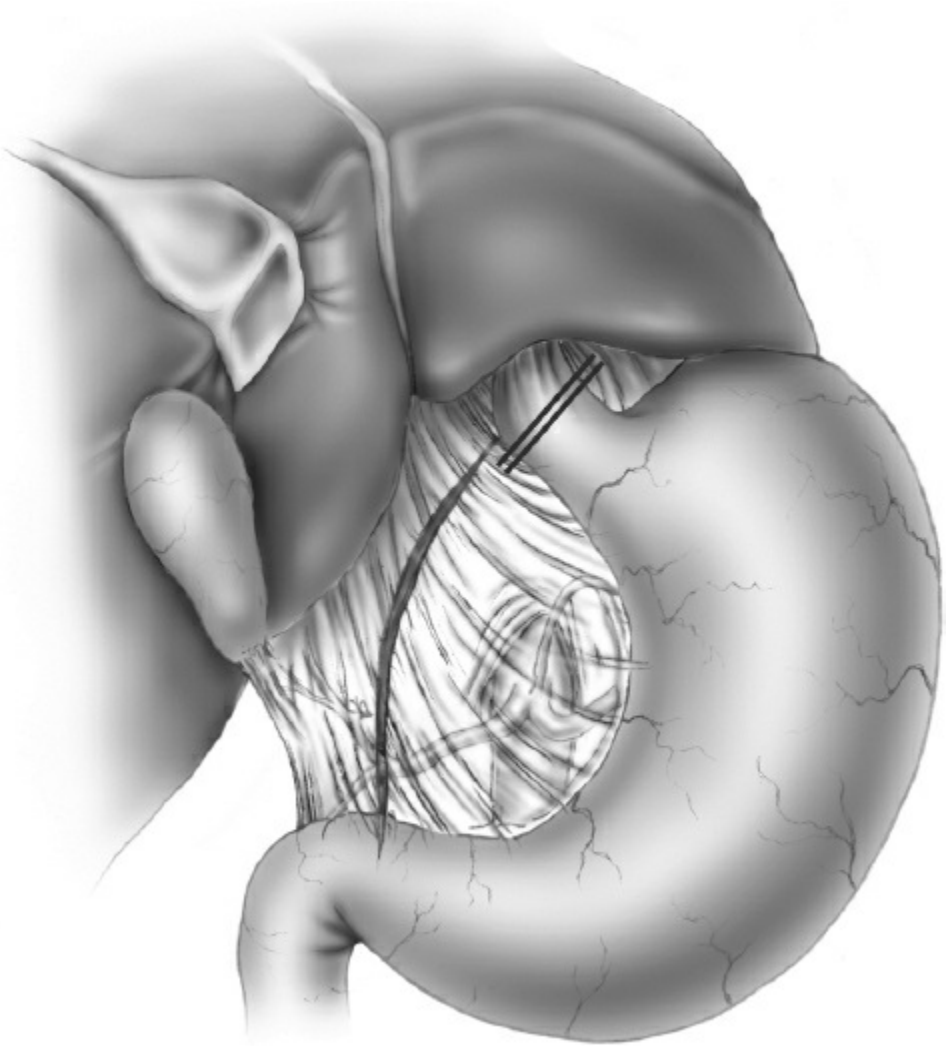

Figure 9.5 Division of the esophagus for total gastrectomy, 2 to 3 cm proximal to the GEJ. (With permission from Paul F. Mansfield, MD.)

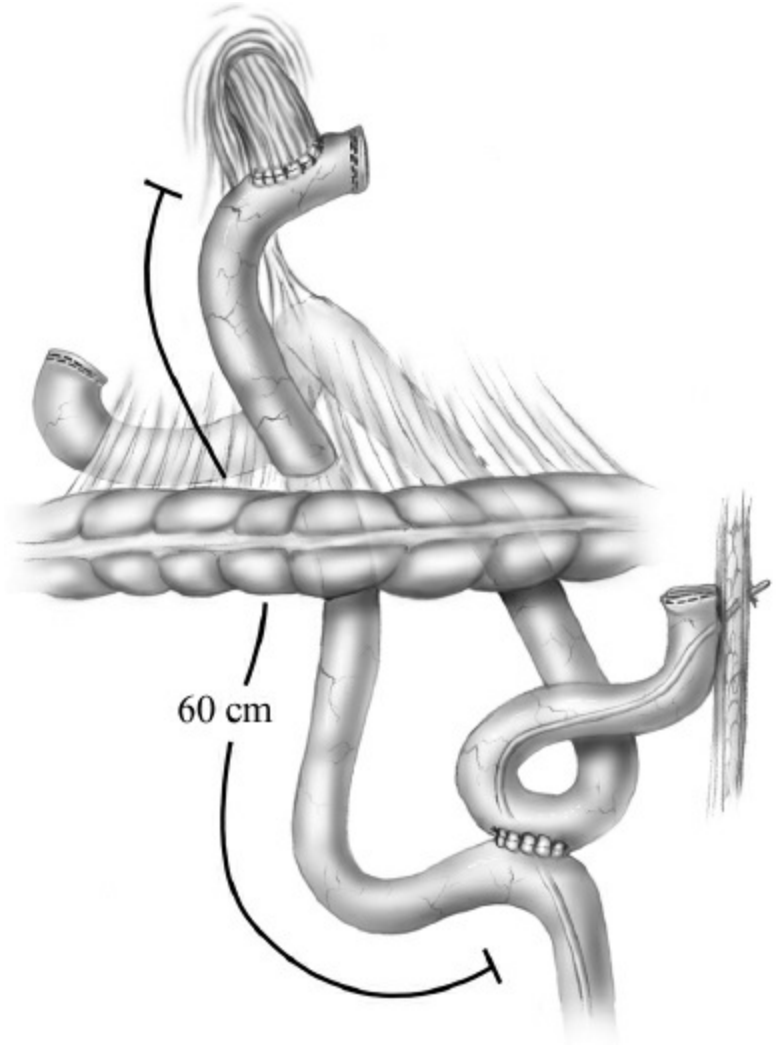

Figure 9.6 Roux-en-Y reconstruction for total gastrectomy, with jejunostomy feeding tube. (With permission from Paul F. Mansfield, MD.)

As experience with the technique grows and the technical aspects of the procedure are refined, laparoscopic resection for gastric cancer is being performed more frequently in both the East and West. However, the technique remains investigational and the long-term oncologic outcomes have yet to be assessed. While circular stapling and flexible stapling devices may make this operation technically feasible, there is some controversy over the safety of the esophagojejunostomy when laparoscopic total gastrectomies are performed. The use of this technique is dependent on the surgeon's minimally invasive skills. Longer-term oncologic outcomes evaluating locoregional disease control and survival will have to be assessed before laparoscopic resection becomes more widely utilized.

SURGICAL OUTCOMES

Complications

Complications from gastric cancer resection are similar to other major abdominal complications and include pulmonary issues, bleeding, infection, cardiac issues, and venous thromboembolism. The rates of major and minor complications are approximately 20% to 30% and 40% to 45% in our most recent series. One of the most potentially devastating complications is an anastomotic leak, which occurs in 2% to 15% of patients. Leaks can occur late in the postoperative course, including after the patient has been discharged home and is presumably doing well; therefore continued vigilance is necessary. Endoscopic techniques, such as the use of covered stents over anastomotic leaks, have been described to manage leaks with good outcomes. Our approach to anastomotic leaks is to attempt to manage conservatively with adequate drainage using percutaneous drains, endoscopic stenting, and nutritional support with jejunostomy feedings. Complications may have long-term effects on oncologic outcomes, thus further emphasizing the need for high-quality, comprehensive care of these patients in experienced centers. With improved anesthesia, preoperative risk stratification, perioperative care, and early recognition and rescue of complications, perioperative mortality has improved after gastrectomy. In the most recent MD Anderson experience, 90 days perioperative mortality was 3%.

Oral feeding is typically started 4 to 7 days postoperatively, often after return of bowel function. Supplemental jejunostomy feedings are started the day after surgery and continued until oral intake is adequate, which usually occurs after discharge. Upper gastrointestinal tract contrast studies are performed on the basis of clinical indications only (e.g., fever, tachycardia, and tachypnea). A total gastrectomy drastically changes the patient’s eating habits. A significant proportion of patients will eventually eat regular meals plus snacks, but this will take time. Patients are counseled preoperatively that their eating habits will never return completely back to their preoperative baseline. Within several months, most patients are able to increase their oral intake capacity and eat larger meals less frequently (three or four meals per day). We utilize nutritional support from registered dieticians heavily in both the immediate postoperative course and in the long-term follow-up for these patients. About 10% of patients will develop clinically significant dumping

syndrome. Early dumping typically occurs 15 to 30 minutes after a meal; signs and symptoms include diaphoresis, abdominal cramps, palpitations, and watery diarrhea. Late dumping is usually associated with hypoglycemia and hyperinsulinemia. The medical management for dumping symptoms should include dietary modification (increased fiber diet, avoidance of concentrated sweets, and avoidance of hyperosmolar liquids) and, if refractory, a somatostatin analog.

Survival

Overall 5-year survival in patients with gastric cancer in most Western series, including the most recent AJCC staging report, is approximately 15% to 20%. The survival rates clearly change for patients with localized versus nodal or metastatic disease. Five-year survival for patients with gastric cancer localized to the stomach exceeds 50%, while patients with nodal disease only have an approximately 20% 5-year survival. Survival in reports from Japan and Asia are usually higher, thought to be related to differences in stage, epidemiologic factors, tumor biology, and medical comorbidities.

The differences in outcomes in Eastern and Western series have been studied extensively to discern to what extent patient factors, treatment factors, and early screening factors play a role in the different outcomes. In a direct comparison of two series from US and Korea, Strong et al. found significant differences in age, BMI, site of tumor (more proximal in the United States), early-stage tumors (more common in Korea), and higher number of lymph nodes identified in Korean patients. After multivariate analysis, the disease-specific survival was still significantly better in Korean patients. The authors noted that it was likely that lower node positivity and early-stage tumors accounted for the differences in disease-specific survival. Outcomes in patients of Asian descent treated in US were compared to Caucasians in a recent SEER analysis, which also found that after controlling for relevant risk factors and treatment differences, survival remained higher for Asian descent patients compared to Caucasian patients.

Locoregional recurrence rates after R0 resection for gastric adenocarcinoma remain high, even after R0 resection. Recurrence patterns are complex and often involve multiple regions, typically classified as locoregional, distant, or peritoneal. Recurrence patterns may be affected by treatment strategy, such as use of preoperative therapies. Data from MD

Anderson demonstrated that in patients treated with neoadjuvant therapy, the most common recurrence sites after potentially curative gastrectomy are peritoneal, followed by locoregional, and liver metastases. Most (~80%) recurrences will occur within 2 years after resection. Median survival after recurrence is a dismal 6 months.

ADJUVANT THERAPY

Patients with localized node-negative gastric cancer have excellent outcomes in both Western and Eastern series with a favorable chance at long-term durable cure. Lymph node involvement, unfortunately, decreases 5-year survival rates by as much as 10% to 30%. Recurrence develops in most patients who undergo a potentially curative resection for gastric cancer. Recurrence patterns are variable (as discussed above), but often involve nonlocoregional failure, for which the only reasonable prevention strategy would be systemic chemotherapy. Adjuvant therapy after potentially curative R0 resection has been studied in numerous patients, with particular interest in improving outcomes for high risk node positive patients.

Adjuvant Chemotherapy

Randomized trials investigating the effects of adjuvant chemotherapy alone on survival after complete resection of gastric adenocarcinoma have produced inconsistent results. Some of the more recent trials are summarized in Table 9.3. The JCOG 8801 trial of adjuvant 5-FU–based chemotherapy showed no survival benefit in early stage (T1 and T2) gastric cancers. A later Japanese trial, the ACTS-GC trial from Sakuramoto et al. demonstrated a survival benefit with an adjuvant oral fluoropyrimidine-based therapy in stage II or III gastric cancer after D2 lymphadenectomy. The CLASSIC study from South Korea, China, and Taiwan compared D2 gastrectomy alone to D2 gastrectomy plus adjuvant capecitabine/oxaliplatin and reported a modest improvement in overall and disease free survival. In the CLASSIC trial, subgroup analysis showed that the survival benefit was limited to node positive patients. Meta-analyses of the available adjuvant trials in general have demonstrated a modest benefit to adjuvant chemotherapy versus surgery alone.

TABLE 9.3

Randomized Controlled Trials of Perioperative Treatment of Gastric Cancer

Author, Trial Name, Journal, Year	Country	Treatment	Survival Difference	Indication	Tumor location % Esophageal % EGJ	% of D2 LND % of R0	% of pT1 Patients	% of pN0 Patients
Cunningham, MAGIC,NEJM 2006	UK	Pre + postop CTx vs. surgery only	5-year OS 38% vs. 11%	c-Stage II/III excluding cT1	Eso: 15% EGJ: 12%	41% 66%[b] (surgery) 60%[b] (chemo)	8% (surgery) 16% (chemo)	27% (surgery) 31% (chemo)
Ychou, FNCLCC/FCD, JCO 2011	France	Pre + postop CTx vs. surgery only	5-year OS 38% vs 24%	All curatively resectable pts	Eso: 11% EGJ: 64%	NA (D2 rec'd) 74% (surgery) 84% (chemo)	[c] 32% (surgery) 42% (chemo)	20% (surgery) 33% (chemo)
Macdonald, INT-0116, NEJM 2001	USA	Postop CRTx vs. surgery only	3-year OS 50% vs. 41%	Stage IB/II/III	Eso: 0% EGJ: 20%	10% (54% D0) 100%	NA (pT1–3 31%)	15%
Bang, CLASSIC, Lancet 2012	Korea China Taiwan	Postop CTx vs. surgery only	3-year OS 83% vs. 78%	Stage II/III	Eso: 0% EGJ: 2%	100% 100%	1%	10%
[a]Lee, ARTIST, JCO 2012	Korea	Postop CTx vs. CRTx	3-year DFS[a] 74% vs.78%	Stage IB/II/III excluding T2N0	Eso: 0% EGJ: NA	100% 100%	22%	31%
Sakuramoto, ACTS-GC, NEJM 2007	Japan	Postop CTx vs. surgery only	3-year OS 80% vs. 70%	Stage II/III excluding T1	Eso: 0% EGJ: NA	100% 100%	0%	11%
[a]Nakajima, JCOG 8801 Lancet 1999	Japan	Postop CTx vs. surgery only	5-year OS[a] 86% vs. 83%	c-Stage IB/II/III	Eso: 0% EGJ: NA	NA 100%[b]	33%	53%

[a]No difference in survival.
[b]Curative surgery rate.
[c]Rate of pT0-2, NA: not documented.
Stage is adjusted to AJCC 8th definition. Stage IB: T1N1, T2N0, Stage II: T1N2, T2N1, T3N0.

Adjuvant Chemoradiation Therapy

Radiation treatment is added to adjuvant therapy regimens in an effort to improve locoregional disease control. Radiation therapy is usually combined with a sensitizing chemotherapy agent such as 5-FU. Radiation alone without any chemotherapy, sensitizing or otherwise, is rarely used outside of the palliative setting. The Southwest Oncology Group national intergroup trial (INT-0116) established the data supporting adjuvant chemoradiation after resection for GEJ or gastric adenocarcinoma. Median overall survival was improved from 27 to 36 months compared to surgery alone. Criticisms of the trial raised concern that most patients underwent what would be considered an inadequate lymph node dissection and perhaps the radiation therapy was simply making up for inadequate surgery; 54% underwent a “D0” dissection. Subsequent reports with longer follow-up continue to support the long-term survival benefit of adjuvant chemoradiation versus surgery alone in the trial.

The ARTIST trial from Korea improved upon the INT-0116 trial in two important areas: (1) operative quality was controlled, with all patients undergoing standard D2 lymphadenectomy and (2) the control arm was treated with active, systemic cisplatin-based chemotherapy. The initial report and subsequent follow-up report found no difference in disease-free

or overall survival between adjuvant chemo alone and adjuvant chemoradiation. However, subgroup analysis found that patients with node-positive disease and intestinal-type pathology had improved disease-free survival with the addition of adjuvant radiation therapy. These findings formed the basis for the next ARTIST trial, which is essentially a repeat of ARTIST in node-positive patients only.

The initial results of the CRITICS trial has been reported in abstract form only at the time of this publication. This trial took a combined perioperative approach to treatment. All patients received neoadjuvant chemotherapy and gastric resection. Postoperatively, patients received either chemotherapy alone or chemoradiation. The initial report shows no difference in 5-year overall survival between the two groups (41.3% vs. 40.9%). A final analysis of the results and subgroup analyses will most certainly be forthcoming to determine what can be learned from this trial.

The role of adjuvant chemoradiation was initially promising, but as more data have evolved from trials with rigorous surgical quality control, the benefit of additional radiation therapy seems to be limited. More studies are needed to define those patients who might benefit from adjuvant chemoradiation therapy.

NEOADJUVANT THERAPY

The use of neoadjuvant chemotherapy in the treatment of gastric cancer evolved from preoperative treatment strategies used for esophageal and rectal cancers. There are several potential advantages of neoadjuvant therapy for gastric cancer. These include theoretical biologic advantages (decreased tumor seeding at surgery) and the opportunity to assess *in vivo* tumor sensitivity to the particular chemotherapeutic regimen. If the tumor responds to the neoadjuvant therapy, the same treatment can be continued postoperatively. Another theoretical advantage is an improved R0 resection rate due to tumor consolidation and decrease in size. By giving the chemotherapy upfront before an operation, one can avoid delays or the inability to tolerate chemotherapy due to deconditioning, malnutrition, or other postoperative complications after operative resection. Micrometastatic disease, which ultimately is the cause of death from gastric cancer, is treated early, prior to development of macroscopic disease. Finally, the interval required for neoadjuvant therapy provides a time in which progression of disease can be evaluated to identify and select out those patients with aggressive disease who would not have

benefited from operative resection. An advantage specific to preoperative radiation therapy is smaller treatment volume and displacement of contiguous structures by the intact tumor leading to reduced radiation therapy toxicity.

There are potential disadvantages to a neoadjuvant treatment strategy. One potential is that patients with initially resectable primary tumors may progress during therapy rendering them unresectable. Whether this is simply a reflection of extremely aggressive disease as most believe or an actual loss of window of opportunity is practically impossible to discern. It is also possible that the toxicity from preoperative treatment may delay operative interventions or increase surgical morbidity. Finally, there is a risk of overtreating patients with early-stage disease, although improved pretreatment staging with EUS minimizes this risk.

Neoadjuvant Chemotherapy

Various combinations of etoposide, cisplatin, 5-FU (ECF), and doxorubicin as neoadjuvant treatment for gastric cancer have been evaluated in several trials. Clinical response rates have ranged from 21% to 31%, and complete pathologic response rates have ranged from 0% to 15%. Multivariate analysis of three phase II trials of neoadjuvant therapy at MD Anderson identified response to neoadjuvant chemotherapy as the single most important predictor of overall survival after such treatment for gastric cancer.

Survival results of the UK Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial were reported in 2006. In this multi-institutional, prospective randomized trial, 503 patients with stage II or higher gastric cancer were randomized to receive perioperative chemotherapy (preoperative chemotherapy followed by surgery followed by additional postoperative chemotherapy) or to undergo surgery alone. Those randomized to the perioperative treatment arm received three cycles of ECF, followed by surgery and then three additional postoperative cycles of ECF. While completion of the preoperative therapy was a respectable 88%, only 42% of patients completed the postoperative portion of treatment even though they had up to 12 weeks after surgery to begin. Both progression-free survival and overall survival were improved in the treatment arm; 5-year survival was 36% in the treatment plus surgery group and 23% in the surgery-only group. Despite these promising results, the MAGIC trial is not without some criticism. First, the trial included

patients with distal esophageal cancers, which may affect the external validity when applied to pure gastric cancer. Second, the staging in this trial may have been suboptimal due to lack of EUS or staging laparoscopy. Finally, only 40% of patients had a D2 lymph node resection. The findings of the French FNCLCC/FFCD trial were similar. In this trial, patients with GEJ or gastric adenocarcinoma were randomized to two or three preoperative cycles of 5-FU and cisplatin, followed by surgery and three to four postoperative cycles, or surgery alone. Five-year overall survival favored the chemotherapy + surgery group (38% vs. 24%). This trial was confounded by a high number of GEJ and esophageal tumors (~75% of the study), so the applicability of its findings to purely gastric adenocarcinoma are unclear. Of course, these studies do not address whether chemotherapy given in a strictly *neoadjuvant* setting improves survival, as the treatments were considered perioperative therapy with cycles given both before and after operative resection.

The EORTC 40954 compared neoadjuvant 5-FU/cisplatin and surgery to surgery alone in locally advanced gastric and GEJ adenocarcinoma. The trial was stopped early for poor accrual; no survival difference was demonstrated in the limited results. Interesting findings from the trial include increased R0 rates in the neoadjuvant group (82% vs. 67%), more lymph node metastases in the surgery alone group (77% vs. 61%), and a nonsignificant trend toward greater postoperative morbidity in the neoadjuvant group (27% vs. 16%).

Neoadjuvant Chemoradiation

Radiation alone is rarely given in the neoadjuvant setting. Most studies report experience with the combination of chemotherapy and radiation therapy in the neoadjuvant setting. The general approach to gastric adenocarcinoma at MD Anderson is to deliver neoadjuvant chemotherapy or more commonly chemoradiation therapy, except in select patients with early, localized cancers. This approach has been built on the basis of our early experiences with 5-FU–based chemoradiation therapy published in the 2000s.

In 2004, Ajani et al. demonstrated that with a three-step multimodality approach consisting of induction chemotherapy (5-FU, leucovorin, and cisplatin), followed by chemoradiation therapy (45 Gy plus concurrent 5-FU), then gastrectomy, a complete pathologic response of 30% can be achieved. The R0 resection rate in the series was 70%. At a median

follow-up of 50 months, the median survival was 33.7 months, and 2-year survival rate was 54%. There were two treatment-related deaths.

Ajani et al. then reported a prospective nonrandomized study of preoperative paclitaxel-based chemoradiation therapy. The neoadjuvant regimen was two cycles of 5-FU, cisplatin, and paclitaxel for 28 days, followed by chemoradiation therapy. All patients underwent gastrectomy with spleen-preserving D2 lymphadenectomy after radiographic and endoscopic restaging. At the time of analysis, 78% of patients had undergone an R0 resection, 20% had a complete pathologic response, and 15% had a partial pathologic response. In this study, R0 resection, pathologic complete response, pathologic partial response, and postsurgical T and N status were factors associated with overall survival. This was followed by a second multi-institutional study evaluating two cycles of FU, leucovorin, and cisplatin followed by concurrent radiation and chemotherapy (infusional FU and weekly paclitaxel). The pathologic complete response rate was 26% with an R0 resection rate of 77%. Pathologic response was a major determinant of outcome.

In our most recent experience at MD Anderson with neoadjuvant chemoradiation therapy for gastric cancer, we reported a series of 195 patients receiving either induction chemotherapy followed by chemoradiation (79%) or chemoradiation alone (21%) followed by gastrectomy with curative intent. An R0 resection was achieved in 93% of patients, and a complete pathologic response was achieved in 20% of patients. Median overall survival was 5.8 years. Nodal status was the most important independent predictor of overall survival. This strategy of preoperative chemotherapy or chemoradiation therapy followed by resection is effective and well tolerated by patients. Concerns about increased postoperative morbidity or failure to continue on to resection are not apparent in our results. The rates of 90-day major and minor complications and mortality are no different in patients undergoing upfront surgery, neoadjuvant chemotherapy, or neoadjuvant chemoradiation therapy. Preoperative therapy is completed by 81% of patients undergoing chemotherapy alone and 93% of patients undergoing chemoradiation. In approximately 25% of patients, progressive, unresectable, or metastatic disease is identified during preoperative therapy—this is a subset of patients that was saved the morbidity of a noncurative operation. Finally, toxicities from chemotherapy (2%) and chemoradiation (6%) rarely result in the inability to undergo operative resection.

METASTATIC DISEASE

Up to 40% of patients will have metastatic disease at the time of their initial presentation, and an additional subset will be deemed unresectable based on local tumor advancement or patient comorbidities. These patients are thus treated not with curative intent but with the goal of symptom relief and palliation to improve not only the duration of their remaining life but the quality as well. Furthermore, a sizable number of patients will recur after definitive surgical resection with metastatic disease and are thus incurable. Palliation is thus an essential set of skills that must be mastered by physicians regularly treating gastric cancer. Optimal palliation relieves or abates symptoms, while causing minimal morbidity and improving the patient's quality of life. Prolonged survival is generally not a goal of palliative treatment, but palliation may relieve debilitating and potentially life-threatening problems, such as gastrointestinal bleeding or gastric outlet obstruction, which may impact short term survival.

Nonoperative Palliation

Systemic chemotherapy can be offered with palliative intent in patients with metastatic or recurrent gastric cancer. Chemotherapy is associated with prolonged survival, with more benefit from combination therapy compared to single agent 5-FU. Aggressive palliative chemotherapy regiments must be balanced with patient expectations, side effects, and expected improvements in quality of life. Radiation therapy can be used to reduce bleeding from unresectable, advanced gastric cancer. Malignant ascites is often a source of patient discomfort and distress in advanced gastric cancer. Repeat therapeutic paracenteses can be performed, possibly with the aid of an indwelling catheter, in certain clinical scenarios.

Operative Palliation

Operative palliation for advanced gastric cancer may involve minimally invasive endoscopic approaches to provide symptomatic decompression or to relieve obstruction. Operative palliative resection, including palliative total gastrectomy, may have a role in carefully selected patients. A thorough understanding of the patient's symptoms, goals, expectations, and systemic therapy options are necessary to decide on the most appropriate approach to operative palliation.

Palliation with endoscopic techniques may be appropriate for patients with peritoneal disease, hepatic metastases, extensive nodal metastases, or ascites and for patients with problems that include bleeding or gastric obstruction. Both morbidity and mortality from these seemingly minimal risk procedures are relatively high in these patients and must be discussed carefully. Laser recanalization or simple dilatation with or without stent placement can be used to treat gastric outlet obstruction. Repeat endoscopy may be required at periodic intervals. Stenting may be used at the GEJ or in distal tumors. Operative gastrojejunostomy is sometimes necessary to adequately address the obstruction and provide symptom relief. A venting gastrostomy tube, placed by either interventional radiology or endoscopy, may be useful for distal gastric outlet obstructions. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered to palliate debilitating malignant ascites.

The selection of patients for palliative gastrectomy is complex. In patients with an excellent performance status, experienced surgeons can perform palliative distal gastrectomy with minimal morbidity and acceptable mortality rates. Palliative total gastrectomy and esophagogastrectomy, however, should be approached with great caution because the morbidity from these procedures is higher. Median survival is less than 1 year in most studies examining palliative gastric resection. Additional palliative procedures after palliative gastrectomy are often necessary. Symptom resolution may be achieved in less than 50% of patients undergoing palliative gastrectomy.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Due to the tendency of gastric cancer to form peritoneal metastases, local therapy with HIPEC with or without cytoreduction has been attempted to either prevent or treat this unique, somewhat localized form of metastatic disease. The technique can be applied to two clinical situations with different treatment goals: (1) a combined cytoreductive surgery (CRS) with HIPEC can be performed at the time of gastrectomy to render a patient with existing macroscopic peritoneal metastases disease-free, or (2) HIPEC can be performed at the time of gastrectomy in an *adjuvant* setting to reduce the risk of peritoneal recurrence in situations in which there is no macroscopic or microscopic evidence of peritoneal metastases, but the primary tumor penetrates the serosa and is considered high risk.

CRS-HIPEC for Metastatic Disease

CRS-HIPEC in combination with gastrectomy for M1 disease localized to the peritoneum should only be considered in carefully selected patients with low-volume peritoneal disease. A complete cytoreduction is associated with improved survival over an incomplete one, thus the procedure should only be undertaken in patients with a low peritoneal cancer index (PCI). Outcomes are best with low PCI and complete cytoreduction. Mitomycin C or oxaliplatin-based regimens have been described. Peritonectomy is associated with high rates of postoperative morbidity and mortality, thus the risk and benefits of aggressive cytoreduction must be weighed carefully. The addition of HIPEC to a cytoreduction alone does appear to improve overall survival in patients with peritoneal metastases without an increase in postoperative morbidity according to a randomized clinical trial reported by Yang et al. Reported 5-year survival rates in most series are still relatively low, in the range of 10% to 30%. However, theses survival rates must be considered in the context of other patients with M1, stage IV gastric cancer. Neoadjuvant systemic and laparoscopic-based HIPEC therapy has also been used in an attempt to reduce the volume of peritoneal disease and improve the rates of complete cytoreduction.

Overall, the reported outcomes for CRS-HIPEC in gastric peritoneal carcinomatosis are underwhelming at best and should caution the surgeon against indiscriminate use of this procedure. A very small benefit may be realized at a potential high cost to the patients. Reported reoperation and postoperative fistula rates are high and hospitalization stays are quite long. With modern, aggressive chemotherapy regimens, similar survival outcomes can be achieved with systemic chemotherapy alone, especially in highly selected patient populations. For these patients, in whom survival time is measured in months, an aggressive, highly morbid operation may not be in their best interest. The concept, however, is appealing and in patients with the right biology, it may offer a reasonable chance of durable response. The use of laparoscopic HIPEC in low volume disease may be the situation in which this technique is best applied. Further investigation will be required to clarify the role of CRS-HIPEC in patients with isolated peritoneal metastases.

Adjuvant HIPEC

For patients with T4 tumors with serosal invasion, the risk of recurrence, particularly peritoneal recurrence, is high, even in patients with negative cytology. As many as one-third of patients may have peritoneal recurrence after resection. Based on these observations, the concept of preemptive or adjuvant HIPEC at the time of gastrectomy is appealing to treat microscopic disease in an effort to reduce peritoneal recurrences. Several small randomized clinical trials have attempted to test this theory. It appears that HIPEC after gastrectomy is safe and does not result in increased postoperative morbidity. The findings regarding the effect of survival, both overall and disease-free, are mixed. A meta-analysis of 10 randomized trials found that HIPEC did significantly improve overall survival and peritoneal recurrence, with a pooled relative risk reduction of 0.73. These findings were consistent in studies that used either mitomycin C or 5-FU, with or without systemic chemotherapy. Larger, multicenter trials are needed to more fully define the role of HIPEC at the time of gastrectomy to reduce the risk of peritoneal recurrence.

GENERAL APPROACH AND FOLLOW-UP

The practice algorithm for the treatment of gastric cancer at MD Anderson can be found online in a continually updated format on the MD Anderson website. A comprehensive initial evaluation is performed to assign a clinical stage, which is the basis on which further workup or treatment is recommended. Early T1a lesions are considered for EMR. Upfront gastrectomy without neoadjuvant therapy is usually only considered in select cases with T1b or T2 disease without any evidence of nodal disease. Otherwise, most patients are evaluated for neoadjuvant chemotherapy or chemoradiation therapy. Restaging is preferred with cross sectional imaging after the completion of neoadjuvant therapy prior to resection. After gastrectomy, node-negative patients may be simply observed or recommended for adjuvant chemotherapy. T3 or greater patients, or those with positive nodes, usually received adjuvant chemoradiation or chemotherapy depending on their neoadjuvant regimen. All patients are evaluated for inclusion in relevant, appropriate clinical trials.

Patients are typically seen every 3 months for the first 2 years following resection. A careful history and physical examination is performed, along with laboratory studies (complete blood cell count, liver function tests, chemistries, prealbumin, vitamin B12, and vitamin D levels). Chest, abdominal, and pelvic CT is performed every 6 months after surgery for 2

years and then yearly thereafter. It is important to balance the intensity of follow-up with the likely ability to benefit a patient who does have a recurrence. In patients who have undergone a subtotal gastrectomy, endoscopy should be considered at the end of the first postsurgical year, once more the following year, and finally once more 5 years after surgery. Patients who receive protocol-based therapy often have more frequent staging studies, but this has never been proven to impact patient survival. Perhaps the most important reasons to follow patients closely are to recognize and address any postgastrectomy sequelae and to acquire accurate recurrence and survival data on patients in clinical trials.

OTHER GASTRIC MALIGNANCIES

Gastric Lymphoma

The gastrointestinal tract is the most common site of extranodal non-Hodgkin lymphoma (NHL). Two-thirds of gastrointestinal lymphomas occur in the stomach, while less than 5% of gastric neoplasms are lymphoma. The two primary histologic types are low-grade marginal zone B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type and high-grade diffuse large B-cell lymphoma (DLBCL); the latter contains a low-grade MALT component in approximately one-third of cases. Whether high-grade lymphomas derive from MALT lymphomas remains unresolved, however the pathogenesis for both is frequently attributed to chronic gastritis and infection with *H. pylori*. The initial symptomatology of gastric lymphoma is often nonspecific and delay in diagnosis is common. The most frequent symptoms at the time of presentation are pain (88%), loss of appetite (47%), weight loss (25%), bleeding (19%), and vomiting (18%). Obstruction and perforation are possible, but uncommon, presenting symptoms.

Diagnosis is established with upper endoscopic evaluation and biopsy. Multiple biopsies should be taken in each region of the stomach, duodenum, and GEJ. All suspicious lesions should be sampled, as well as normal-appearing mucosa. Deeper biopsies, including possible EMR, may be necessary to establish the diagnosis. The presence of *H. pylori* must be determined through histopathology, urease enzyme levels (breath test), and serology. Testing for the t(11;18) translocation should be performed in cases of MALT lymphoma, as its presence is associated with resistance to certain treatments, including *H. pylori* eradication. Laboratory evaluation

includes lactate dehydrogenase and beta-2-microglobulin levels as well as bone marrow aspiration and biopsy. The extent of disease is assessed with cross sectional imaging of the chest, abdomen, and pelvis.

The general trend over the last several decades has been away for surgical treatment for gastric lymphoma and toward nonsurgical therapy. Initial therapy for early-stage, low-grade MALT lymphoma consists of regimens of antibiotics and proton pump inhibitors for the eradication of *H. pylori* and results in long-term remission in a majority of patients. Assessment of failure of MALT lymphoma to resolve with *H. pylori* eradication can only be made after several years, as the median time to tumor remission is 15 months. Serial endoscopic evaluation is used to assess response. There is evidence that patients with limited residual disease may either be safely observed or treated with an alternative *H. pylori*-directed therapy. Patients with the t(11;18) translocation are often resistant to *H. pylori* eradication and may need to be treated with multimodality therapy.

For patients with persistent MALT lymphoma after *H. pylori* therapy or those without evidence of *H. pylori* infection, external beam radiation therapy has a 90% to 100% rate of complete response and results in durable remission in a majority of patients. Alternatively, single-agent chemotherapy or rituximab (anti-CD20 monoclonal antibody) may be administered if radiation is contraindicated or may be preferential to receiving radiotherapy to minimize impact on future treatment options should a patient subsequently develop a gastric or GEJ adenocarcinoma (which we have seen on several occasions). Combination chemotherapy, often combined with rituximab, is reserved for patients with GI bleeding, bulky local disease, or progressive systemic disease. Close monitoring without treatment is also an option in asymptomatic patients with medical comorbidities that preclude aggressive radiation or systemic therapy.

DLBCL is the most common type of gastric lymphoma. Treatment varies but typically consists of aggressive anthracycline-based combination chemotherapy, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and R-CHOP (with rituximab). The addition of operative resection to systemic chemotherapy does not improve survival. In patients with gastric DLBCL containing a low-grade MALT component, *H. pylori* eradication can result in complete response and sustained remission. The role of consolidation radiotherapy remains unclear. Retrospective studies suggest that patients with localized disease

(stages I and II) may have lower local relapse rates with the addition of consolidation radiotherapy. The development of these regimens has resulted in a significant improvement in overall survival rates. Patients who relapse are treated with high-dose chemotherapy followed by autologous stem-cell transplantation.

Currently, the most common indications for surgical intervention in gastric lymphoma include bleeding, perforation, obstruction, and the rare finding of localized residual disease after primary therapy. While operative resection historically has demonstrated excellent outcomes for gastric lymphoma, it has largely been abandoned in favor of chemotherapy and radiation regimens with comparable oncologic outcomes and superior quality of life results. Complications requiring operative intervention during treatment for gastric lymphoma are rare (~5%). Patient with large, bulky, transmural tumors are those at greatest risk of treatment-related complications such as perforation. In these patients, a dose reduction for the first cycle of chemotherapy may be used as a precaution while the patient is carefully observed for complications.

Neuroendocrine Tumors (NET)

Gastric NET constitute less than 10% of all NETs, but the incidence is increasing in the United States. Whether this is due to the increased use of endoscopy and subsequent increased number of asymptomatic tumors being diagnosed or an actual increase in the incidence of these tumors is unclear. Four distinct types of gastric NETs have been described with variable clinical courses and prognosis. Gastric NETs are also graded by WHO criteria into three classifications: well-differentiated (carcinoid), well-differentiated neuroendocrine carcinoma (malignant carcinoid), and poorly differentiated neuroendocrine carcinoma.

Type 1 gastric NETs are the most frequent, accounting for 70% to 80% of all cases. Typically these are asymptomatic, small (usually <1 cm), well differentiated, and multifocal. The majority of patients are women (70% to 80%) and the condition develops in the setting of chronic atrophic gastritis and enterochromaffin-like (ECL) cell hyperplasia. These patients have elevated plasma gastrin levels and low gastric acid production. Regional lymph node metastases are rare and usually occur only in larger tumors that penetrate the muscularis propria. Endoscopic resection is the treatment of choice for small tumors (<2 cm). Surgical excision or resection is considered for larger or more invasive tumors. Endoscopic surveillance

alone is also an option in small, asymptomatic tumors. Type 1 tumors have a tendency to recur and larger, more advanced tumors may be associated with concomitant adenocarcinoma, so careful, long-term endoscopic surveillance is required. These patients have an excellent prognosis with 5- and 10-year survivals that are comparable to the general population.

Type 2 gastric NETs are associated with multiple endocrine neoplasia type 1 (MEN-1)–associated Zollinger–Ellison syndrome (ZES). They account for 5% to 6% of gastric endocrine tumors. These tumors rarely develop in sporadic ZES patients (<0.1%), however they are relatively common in MEN-1/ZES patients (15% to 30%). The disease tends to develop late in the course (15 to 20 years) of MEN-1/ZES disease. The tumors are typically well differentiated, multifocal, small (<1.5 cm), and limited to the mucosa/submucosa. ECL hyperplasia is common. These patients have elevated plasma gastrin levels and high gastric acid production. In tumors larger than 2 cm or with invasion of the muscularis propria, there is up to a 30% incidence of regional lymph node spread or metastatic disease. Therapy is directed toward localizing and removing the source of hypergastrinemia; most commonly this requires local excision of the gastrin-producing duodenal or pancreatic gastrinoma. Somatostatin analogs are used to inhibit tumor growth, particularly in patients in whom hypergastrinemia cannot be surgically corrected. Resection of type 2 NETs is reserved for tumors with suspicious or proven signs of malignancy. Type 2 gastric NET patients have 5-year survival rates of 60% to 75%.

Between 14% and 25% of gastric NETs are type 3. These are more aggressive sporadic neoplasms not associated with ECL hyperplasia, hypergastrinemia, or any other diseases of the stomach. They are more common in males. The tumors tend to be solitary, large (3 to 5 cm), and are well differentiated. Plasma gastrin levels and gastric acid production are usually within normal limits (though the use of proton pump inhibitors may impact this and should be accounted for during evaluation). Penetration of the muscularis propria is common and invasion of all layers of the gastric wall is seen in approximately 50% of patients. Metastases are present in greater than 50% of patients with larger lesions. Treatment is similar to gastric adenocarcinoma and consists of operative resection to achieve negative margins, lymph node dissection, and consideration of systemic chemotherapy. Because of the generally favorable biology of these tumors, aggressive surgical or ablative therapies should be considered, as reasonably prolonged overall survival is reported, even in

patients with metastatic disease.

Type 4 gastric NET is the newest classification and accounts for 6% to 8% of gastric NETs. These tumors occur more frequently in men and consist of highly malignant, poorly differentiated (small cell) neuroendocrine carcinoma. Patients commonly present at an advanced stage with large (>5 cm), often ulcerated primary masses exhibiting local invasion and often have metastases. As such, surgical intervention is rarely appropriate for these patients, but may be considered in the rare event of localized disease.

Systemic chemotherapy has limited efficacy in metastatic gastric NETs. Most studies have evaluated treatments for metastatic NETs from multiple primary sites. Somatostatin analogues have been evaluated in metastatic settings with some improvement in time to tumor progression. Everolimus has an impact on the survival of patients with pancreatic NETs, but there are limited data reporting its efficacy in gastric NETs.

Our general approach to gastric NETs at MD Anderson take into account the type of NET, WHO grade, and patient comorbidities. For type 1 and 2 gastric NETs, operative resection is recommended for NETs greater than 2 to 3 cm in diameter. Because of the indolent nature of type 1 and type 2 gastric NETs, nonsurgical management may be preferable in older patients or those with significant comorbidities. Somatostatin analogs can promote the regression of small (<1 cm) gastric NETs and may also prevent recurrence after resection. When complete R0 resection is achievable, aggressive surgical and/or ablative therapy may be considered in carefully selected type 1, 2, and 3 patients with metastatic disease.

CONCLUSION

Gastric cancer demands a thoughtful, multidisciplinary approach in order to achieve successful long-term outcomes. Durable cure may only be possible in a minority of patients in whom early gastric cancer is identified. However, all patients with gastric cancer can benefit from evaluation by an experienced surgeon in conjunction with a multidisciplinary team to formulate a comprehensive treatment plan that meets each patient’s needs and goals. New therapies, including the promise of immunotherapy, continue to be evaluated in gastric cancer. The surgeon will always play an essential role in the diagnosis, staging, and treatment of this disease.

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10 Small Bowel Malignancies

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INTRODUCTION

Small bowel malignancies represent a rare malignancy. They affected an estimated 10,090 individuals in the United States (US) in 2016, with 1,330 people dying from the disease. There are multiple histologic types of primary small bowel malignancies, the most common being adenocarcinoma, carcinoid, sarcoma, and lymphoma. Metastases from other tumor types such as melanoma, lung, colon, and ovarian cancers are also seen. This chapter will focus on the most common primary small bowel malignancies (adenocarcinoma, carcinoid, lymphoma, and sarcoma).

EPIDEMIOLOGY

The incidence of small bowel cancers is rising. In the US, the incidence of small bowel cancers has increased from 11.8 cases per million in 1973 to 22.7 cases per million in 2004 (Bilimoria et al.). African Americans in the US have the highest age-adjusted incidence of small bowel cancers in the world (Haselkorn et al.).

Historically, adenocarcinoma accounts for 30% to 50% of small bowel malignancies, carcinoid 20% to 30%, and lymphomas and stromal tumors 15% each. However, a study by Bilimoria et al. using the National Cancer Data Base (NCDB, 1985–2005) and the Surveillance Epidemiology and End Results (SEER, 1973–2004) database found that of the 67,843 patients identified, 37.4% had carcinoid, 36.9% adenocarcinoma, 17.3% lymphoma, and 8.4% stromal tumors. The rise in the incidence of carcinoid tumors in US was from 2.1 per million in 1973 to 9.3 per million in 2004, representing a 340.5% increase. The reason for the rising incidence is unclear but may be related to increased detection rate.

When broken down into the different anatomic regions of the small

bowel, carcinoids are more common in the ileum while adenocarcinomas are more often found in the proximal small intestine. Sarcomas and lymphomas are most commonly seen in the distal small bowel but can be found throughout.

RISK FACTORS

The small intestine accounts for 75% of the length of the gastrointestinal (GI) tract but small bowel malignancies encompass <5% of all GI cancers. Protective factors released by the small intestine, stool quality, and low levels of carcinogenic factors may explain this discrepancy. Another factor thought to contribute to the relative low incidence is secretion of immunoglobulin A by the small intestine, which provides an integral role in mucosal immunity.

Familial inherited syndromes are also associated with small bowel cancers. These include familial adenomatous polyposis, Peutz–Jeghers, Lynch syndrome, Cowden syndrome, von Recklinghausen neurofibromatosis, and Crohn disease.

CLINICAL PRESENTATION

Patients with small intestine malignancies are more likely to present with GI complaints compared to patients with benign lesions. Common presenting symptoms include abdominal pain (75%), weight loss (28%), bowel obstruction (25%), and bleeding (24%). Duodenal cancers can present with jaundice if the ampulla is involved. Diagnosis is often delayed unless the presentation involves an emergent situation such as obstruction, bleeding, or perforation. Bowel perforation is the presenting symptom in 10% of patients and is more often seen with lymphoma or sarcoma.

DIAGNOSTIC WORKUP

Initial workup consists of performing a comprehensive history and physical examination. Labwork should include a complete blood count, serum electrolytes, liver enzymes, and 5-hydroxyindoleacetic acid (5-HIAA) if there is clinical suspicion for a carcinoid tumor.

Cross-sectional imaging is frequently utilized for diagnosis. Computed tomography (CT) imaging carries a sensitivity of 80% for small bowel lesions and increases to 85% to 95% with CT or MR enterography

(Pappalardo et al. and Pilleul et al.). For carcinoid tumors, radio-labeled somatostatin analog [^{111}In-DTPA^{0}] octreotide scintigraphy (OctreoScan) can be used as an adjunct for identification of the primary and extra-abdominal lesions, carrying a sensitivity of 88% and specificity of 97% (Pape et al.).

Endoscopy allows for the detection and biopsy of proximal small bowel malignancies in the duodenum, however evaluation of lesions in the more distal small bowel are challenging. Single and double balloon enteroscopy are modalities to examine beyond the ligament of Treitz. A study by Takano et al. compared single to double balloon enteroscopy and found higher rates of completion of total enteroscopy with double balloon (0% vs. 57%, p = 0.002) but no difference in therapeutic outcomes (single balloon 28% vs. double balloon 35%, p = 0.63). Use of single or double balloon enteroscopy is still based on physician preference and availability.

Video capsule endoscopy (VCE) is another modality that is increasingly being used to evaluate the small intestine. A pill-shaped camera is ingested and transmits images of the entire small intestine. A pooled meta-analysis by Lewis et al. found a lower rate of missed pathology compared to enteroscopy with equivalent completion rate. VCE has poor diagnostic yield when used in patients with delayed gastric emptying, previous abdominal operations, and poor bowel preparation. Risks with VCE include retention of capsule requiring either repeat endoscopy or operation in 1% of patients.

Despite the multiple diagnostic tools available, an accurate diagnosis of small intestinal malignancy remains difficult and is only made in half of cases. When no diagnosis has been made but clinical suspicion is high and patients have symptoms of GI bleeding or obstruction, exploratory laparotomy should be performed and intraoperative endoscopy can be done with surgeon assistance allowing for complete visualization of the small intestine. Diagnostic laparoscopy can also assist in surveying the peritoneal cavity and obtaining biopsies when GI complications are absent.

SPECIFIC TYPES OF SMALL BOWEL MALIGNANCIES

Adenocarcinoma

Pathology

Small bowel adenocarcinomas (SBAs) historically accounted for 30% to 50% of all small bowel malignancies but contemporary studies have found

rates of 36.9%, dropping to the second most common primary small intestinal malignancy behind carcinoid tumors. Over half of these lesions arise in the duodenum, followed by the jejunum and ileum. Much like colorectal adenocarcinoma, these tumors can enlarge, invading through the serosa to adjacent structures. Tumor enlargement can cause obstructive symptoms or, with a duodenal primary, gastric outlet obstruction. Violation of the mucosal layer can lead to gastrointestinal bleeding or chronic anemia.

Genetic analyses reveal mutations in several key genes. The adenomatous polyposis coli (*APC*) gene is mutated in 10% to 18% of SBA compared to 80% of sporadic colorectal cancers (CRC) (Wheeler et al., Arai et al.). Although *APC* is mutated in both, studies examining mutational profiles found they differ between CRC and SBA, suggesting the pathway to adenocarcinoma is not the same between small and large bowel adenocarcinomas.

Germline mutations in the *APC* gene are found in familial adenomatous polyposis (FAP). Patients with FAP develop duodenal adenomas in 80% of cases with 4% developing adenocarcinoma (Vasen et al.). Due to the risk of malignant transformation, endoscopic surveillance is required.

Lynch syndrome is associated with germline inactivation in one or more of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), leading to microsatellite instability. This inactivation is found in over 90% of Lynch syndrome patients. Sporadic mutations, particularly in *MLH1*, can also occur with overall inactivation of the mismatch repair (MMR) system occurring in 15% of CRC. SBA have deficiency in MMR (dMMR) in up to 35% of cases, much higher than that in colorectal adenocarcinoma, once again suggesting the molecular mechanisms behind the development of SBA are different from large bowel adenocarcinomas (Overman et al.). SBA patients with dMMR are more likely to have lesions localized to the proximal (duodenum, jejunum) rather than distal small intestines.

Additional important proteins frequently mutated in SBA are *KRAS* and p53, with mutation rates as high as 53% and 52%, respectively.

Staging

The American Joint Committee on Cancer (AJCC) eighth edition staging for small bowel adenocarcinoma is shown in Table 10.1.

Clinical Course

The clinical symptoms of SBA are often nonspecific, therefore more than half of patients present with stage III or IV disease. Prognosis is based on the stage of disease with 5-year overall survival rates of 50% to 60% for stage I, 39% to 55% for stage II, 10% to 40% for stage III, and 3% to 5% for stage IV (Aparicio et al.). Compared to other small bowel malignancies such as carcinoid, lymphoma, and stromal tumors, SBA have a poorer prognosis.

Lymph node metastasis are present in 35% of patients at the time of diagnosis and 20% will have distant disease, with the liver being the most common location. A SEER database study by Overman et al. examining the prognostic value of lymph nodes in SBA found that there was a survival benefit with a greater total number of lymph nodes examined for stage I–III disease. Furthermore, in patients with stage III disease, there was a poorer 5-year disease-specific survival when ≥3 positive lymph nodes were found compared to <3 (37% vs. 58%).

Tumor markers for SBA are similar to large bowel adenocarcinoma and include carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). CEA and CA 19-9 are elevated in 30% and 40% patients, respectively (Raghav et al.). These markers can be used as prognostic factors for progression free/overall survival and to monitor for disease recurrence.

Surgical Treatment

The primary treatment for SBA involves complete resection with locoregional lymphadenectomy. Patients with unresectable disease have a 5-year overall survival of 0% compared to 54% for resectable disease.

Proximal duodenal lesions are managed with pancreaticoduodenectomy with locoregional lymphadenectomy. For distal duodenal lesions, wide excision with lymphadenectomy may be appropriate as long as negative margins are obtained. Jejunal and ileal lesions are typically treated with wide excision and regional lymph node dissection. For ileal lesions close to the cecum, a right colectomy or ileocecectomy may be required in order to obtain negative margins.

TABLE 10.1 AJCC Eighth Edition Staging for Small Bowel Cancer, Excluding Lymphomas, Carcinoid, and Visceral Sarcomas

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)
Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 or 2 regional lymph nodes
N2	Metastasis in 3 or more regional lymph nodes
Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis is present

Staging	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	Any T	N1	M0
Stage IIIB	Any T	N2	M0
Stage IV	Any T	Any N	M1

AJCC, American Joint Committee on Cancer.

Adjuvant Therapy

Recurrence after resection for SBA can be as high as 39% lending credence to the argument for adjuvant therapy. Of those with recurrences, 56% are distant, 19% are carcinomatosis, and 17% are local (Dabaja et al.). Prospective randomized data examining the optimal adjuvant regimen for SBA is lacking, with current recommendations guided primarily by retrospective data. Despite the lack of high-quality data, a National Cancer Database study found the rate of adjuvant chemotherapy use has increased from 8% in 1985 to 22% in 2005 ($p < 0.0001$). Based on what data is

available, 5-fluorouracil–based chemotherapy is the standard for patients with high risk SBA (+ lymph nodes) (Raghav et al.).

To address this paucity of data for adjuvant therapy, the International Rare Cancers Initiative (IRCI) was created. This is a joint initiative between Cancer Research UK (CRUK), the National Institute of Health Research Clinical Research Network: Cancer (NIHR CRN:Cancer), the National Cancer Institute (NCI), the European Organization for Research and Treatment of Cancer (EORTC), the Institut National Du Cancer (INCa) and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), whose aim is to "facilitate the development of international clinical trials for patients with rare cancers in order to boost the progress of new treatments for these patients." For SBA, the BALLARD study is a large prospective randomized trial specifically evaluating the impact of adjuvant chemotherapy for small intestinal adenocarcinomas (Keat et al.).

HIPEC

Hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery (CRS) is the standard of care for pseudomyxoma peritonei, peritoneal mesothelioma, and colorectal cancer with peritoneal only metastases, but is emerging as therapy for highly selected patients with SBA. In a study examining prognostic factors for SBA from MDACC, 25% of patients with stage IV disease were found to have peritoneal carcinomatosis. For this highly selective group of patients HIPEC/CRS has a potential role in treatment. This technique involves removing all visible peritoneal disease and perfusing the abdominal cavity with heated chemotherapy.

In a multi-institutional study from the Netherlands by van Oudheusden et al. examining HIPEC/CRS for SBA, complete resection was obtained in 93.8% with median overall survival of 30.8 months versus 7.1 months in patients not undergoing resection.

At MDACC, the treatment algorithm for patients with metastatic SBA with peritoneal-only disease is as follows: (1) patients are discussed at a multidisciplinary tumor board with evaluation of the extent of disease, (2) systemic chemotherapy is started, (3) evaluation for progression via cross-sectional imaging and/or diagnostic laparoscopy, and (4) if there is no progression and the limited disease is amenable to complete resection, HIPEC with CRS is offered.

Metastatic Disease

Systemic chemotherapy is the primary treatment for patients with metastatic SBA. Data from retrospective studies have found improved overall survival with systemic chemotherapy, 13 months versus 4 months ($p = 0.02$) (Czaykowski et al.). These studies used a wide variety of agents but standard therapy should entail use of CAPOX (capecitabine and oxaliplatin) or FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin). Ongoing clinical trials are currently investigating use of this backbone with bevacizumab, irinotecan, panitumumab, erlotinib, and paclitaxel to help determine optimal therapy for metastatic SBA.

Carcinoid Tumors

Epidemiology

Neuroendocrine tumors (NETs) are a diverse group of tumors that arise from enterochromaffin cells found throughout the body. They can arise from the foregut, midgut, or hindgut and have the ability to secrete various hormones and peptides leading to functional syndromes.

The peak incidence of carcinoid tumors is in the seventh to eighth decades. For jejunal/ileal NETs higher rates occur in males compared to females (0.8 vs. 0.57/100,000) (Yao et al.). Small bowel carcinoids account for 42% of NETs of the GI tract and most commonly arise from the terminal ileum. Overall, the incidence of small bowel carcinoids is increasing, with a rise of 2.1 to 9.3 per million from 1973 to 2004 based on SEER data. Small bowel NETs have overtaken SBA as the most common primary tumor of the small intestine.

Risk factors for the development of SB carcinoids includes having a family history of prostate or colorectal cancer among any first-degree relatives; tongue or mouth cancer in siblings; and endometrial, kidney, skin, or non-Hodgkin lymphoma in parents (Boudreaux et al.).

Environmental risk factors for development of carcinoid tumor are unclear. Cigarette smoking was found to increase the risk of developing small bowel carcinoid in a European population-based case-control study, but not in a US-based case-control study, while alcohol consumption did not increase the risk in either study.

TABLE

Neuroendocrine Tumor (NET) of Midgut Grading

10.2 System

Grade	Differentiation	Traditional	ENETs, WHO	Criteria
Low grade	Well differentiated	Carcinoid tumor	Neuroendocrine tumor grade 1 (G1)	<2 Mitoses/10 high-power fields, and <3% Ki-67 index
Intermediate grade	Well differentiated	Carcinoid tumor	Neuroendocrine tumor grade 2 (G2)	2–20 Mitoses/10 high-power fields, or 3%–20% Ki-67 index
High grade	Poorly differentiated	Small cell carcinoma Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), small cell carcinoma Neuroendocrine carcinoma grade 3 (G3), large cell carcinoma	>20 Mitoses/10 high-power fields or >20% Ki-67 index

ENET, European Neuroendocrine Tumour Society; WHO, World Health Organization.
Adapted from Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas* 2010;39(6):753–766.

Pathology

Multiple nomenclature systems exist when describing NETs adding to the confusion and limiting applicability of data when different systems are used.

In an effort to standardize terminology, the European Neuroendocrine Tumor Society (ENETS) and World Health Organization established criteria to ensure clinicians are referring to the same tumor subtype. Based on these criteria, small bowel NETs are differentiated into three grades based on the number of mitosis and Ki-67 proliferative index (Table 10.2). The term "Carcinoid tumor," specifically refers to low/intermediate grade tumors, well-differentiated tumors, or neuroendocrine tumor grades 1 and 2 (also rare well-differentiated grade 3 tumors).

As a whole, at the time of presentation, regional lymph node involvement is seen in 70% of patients and liver metastasis in over half.

submucosal nodules, and are capable of releasing biologically active substances such as serotonin, amines, and prostaglandins. Because multiple tumors are often found, careful evaluation of the entire small bowel is needed during the time of operation.

Staging

The American Joint Committee on Cancer (AJCC) eighth edition staging for carcinoid tumors is shown in Table 10.3.

TABLE 10.3 AJCC Eighth Edition Staging for Small Bowel "Carcinoid" Tumors (Neuroendocrine Tumors Grade I and II, and Rare Well Differentiated Grade III) Arising from the Jejunum and Ileum

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1[a]	Tumor invades lamina propria or submucosa and size ≤1 cm
T2[a]	Tumor invades muscularis propria or size >1 cm
T3[a]	Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4[a]	Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures
Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis less than 12 nodes
N2	Large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels
Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Staging	T	N	M
Stage I	T1	N0	M0
Stage III	T1	N1, N2	M0
Stage IV	T1	N0, N1, N2	M1
Stage II	T2	N0	M0
Stage III	T2	N1, N2	M0
Stage IV	T2	N0, N1, N2	M1
Stage II	T3	N0	M0
Stage III	T3	N1, N2	M0
Stage IV	T3	N0, N1, N2	M1
Stage III	T4	N0	M0
Stage III	T4	N1, N2	M0
Stage IV	T4	N0, N1, N2	M1

[a]For ant T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1–4, and # = number of primary tumor identified[b]]; for multiple tumors with different T, use the highest.
[b]*Example*: If there are two primary tumors, only one of which invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal), we define the primary tumor as either T3(2) or T3(m).
AJCC, American Joint Committee on Cancer.

Clinical Presentation

Carcinoids of the small bowel are typically indolent; this can lead to a delay in diagnosis with many patients having symptoms on average for 5 years before the diagnosis is made. As with SBA, the majority of these patients present with nonspecific chronic abdominal pain and/or obstruction.

Twenty to thirty percent of patients can present with carcinoid syndrome. Carcinoid syndrome symptoms include flushing (94%), watery diarrhea (80%), wheezing, abdominal pain, and pellagra (niacin deficiency). Flushing can be triggered by the consumption of alcohol, blue cheeses, chocolate, or red wine. Long-term carcinoid syndrome can ultimately lead to development of right-sided heart failure (carcinoid heart disease).

The most extreme manifestation of carcinoid syndrome is a carcinoid crisis. Symptoms include hemodynamic instability, shock nonresponsive to vasopressors, hyperthermia, arrhythmia, and/or bronchoconstriction. Those individuals at greatest risk of developing carcinoid crisis are patients with flushing and large bulky tumors. Carcinoid crisis can be triggered by surgery and therefore all patients with NETs should be given octreotide preoperatively.

Diagnosis

The diagnosis of carcinoid tumors is made by the clinical picture, biochemical testing, and imaging.

Chromogranin A (CgA) is a polypeptide present in the secretory granules of neuroendocrine cells. CgA is elevated in 60% to 100% of patients with functional or nonfunctional NETs and have sensitivity and specificities of 70% and 100%, respectively. False elevations in CgA can be seen with renal/liver failure, patients with chronic gastritis, and those taking proton pump inhibitors (PPI). PPIs should be stopped 2 weeks before CgA evaluation.

One of the major hormones released by carcinoid tumors is serotonin, which is metabolized by the liver into 5-hydroxyindoleacetic acid (5-HIAA) and then excreted into the urine. Direct measurement of serum serotonin levels can be inaccurate as there is significant daily variation based on stress and activity level. Twenty-four–hour urinary 5-HIAA levels provide a more accurate measurement of serum serotonin activity. Elevations are found in over half of patients and carry specificity as high as 88% for carcinoid tumors. However, like CgA, 5-HIAA can be falsely

elevated, with incorrect results seen after recent consumption of alcohol, nuts, tomatoes, and cold/cough remedies (Tormey et al.).

Because CgA and 5-HIAA levels can be reflective of overall tumor burden, they can be followed to detect tumor recurrence after initial resection.

In situations where 5-HIAA is not elevated, additional testing should consist of measurements of urinary 5-hydroxytryptamine (5-HT, serotonin) and 5-hydroxytryptophan (5-HPT), plasma 5-HPT, platelet 5-HT, and serum levels of CgA, neuron-specific enolase (NSE), substance P, and neuropeptide K.

Cross-sectional imaging with CT or MRI can identify small bowel carcinoid tumors, having sensitivities of 77% to 80%. NETs are vascular lesions and CT imaging should be done with thin slices with an arterial and late venous phase in order to identify arterial enhancement and venous washout; this is especially helpful in cases of liver metastases. On MRI, carcinoid tumors can have a variable appearance on T1-weighted images, being hypointense or isointense while liver metastases typically appear bright on T2-weighted images.

With any imaging modality used, approximately 25% of patients will have underestimation of the extent of disease (Chambers et al.). OctreoScan can be used as an adjunct to CT or MRI in the identification of locoregional or distant disease. It carries sensitivity as high as 90% and unlike localized cross-sectional imaging, it examines the entire body for occult lesions. OctreoScan identifies somatostatin receptors 2 and 5 in tumors. In some cases, patients with poorly differentiated NETs have lost these receptors and these lesions cannot be detected with OctreoScan.

Treatment of Localized Disease

Complete resection of the primary tumor with regional lymphadenectomy is standard therapy for localized disease.

Prior to any surgery, patients with symptoms of carcinoid syndrome should be pretreated with subcutaneous octreotide (250 to 500 μg) to avoid precipitating a carcinoid crisis (Parris et al.). Additional doses should be available to be given during times of tumor manipulation.

Regional lymph node involvement is seen in 70% of patients; therefore mesenteric resection is mandated not only for purposes of complete resection but also for local control. This can be challenging as small bowel carcinoids can create a significant desmoplastic reaction resulting in

contraction and foreshortening of the mesentery. When mesenteric resection is possible but not accomplished, the remaining lymph nodes can eventually cause obstruction or intestinal ischemia due to thrombosis of mesenteric vessels. As small bowel carcinoids are often multicentric, the entire small bowel should be inspected for disease.

Consideration should be given to performing a prophylactic cholecystectomy in patients who will be placed on long-term somatostatin analogs given the risk of cholestasis and cholelithiasis associated with this medication.

In patients undergoing complete resection for localized, node-negative small bowel carcinoids, median overall survival is 111 months while it is 105 months in those with regional disease (Yao et al.).

Treatment of Advanced Disease

Resection of carcinoids tumors even in the setting of metastatic disease may have a role in palliation, symptom relief, and locoregional control.

If metastatic disease is present and complete resection of all lesions is possible, an attempt should be made to completely extirpate all diseases as it can prolong disease-free survival and provide symptomatic relief. In patients with liver metastases, a partial or complete relief of symptoms can be achieved in 82% of patients after resection of all lesions. As with localized disease, preoperative octreotide should be administered to prevent a carcinoid crisis and a prophylactic cholecystectomy considered given the need for long-term octreotide.

Patients with unresectable metastatic disease who are asymptomatic should be followed with surveillance. Palliative resection can then be offered if they develop tumor related complications such as bleeding, obstruction, or perforation.

For symptomatic patients with hepatic metastases unable to be completely resected and refractory to medical management, liver directed ablative therapies or surgical debulking can help palliate symptoms.

Somatostatin analogs can be used for symptom relief and disease stabilization. The PROMID study, a double-blind randomized controlled trial, compared octreotide LAR (long-acting release) versus placebo in treatment-naive patients with midgut NETs. The study found that treatment with octreotide LAR prolonged median time to progression (14.3 months vs. 6.0 months) (Rinke et al.). In another review of 15 studies by Modlin et al. examining treatment of NETs with octreotide LAR, symptom

improvement was seen in 74% and tumor response in 70%.

For patients with symptoms refractory to somatostatin analogues, interferon-alpha (IFNα) has been shown to reduce diarrhea in 50% of cases, however, the relief was transient.

Combination treatments with somatostatin analogues and systemic chemotherapy have been examined. The RADIANT-2 trial was a phase 3, double-blind placebo-controlled study in patients with advanced NETs and carcinoid syndrome evaluating the effect of everolimus, an inhibitor of the mammalian target of rapamycin (mTOR). Patients were randomized to receive either the combination of everolimus plus octreotide LAR or placebo and octreotide LAR. The study found an improvement in progression free survival from 11.3 months to 16.4 months for the group receiving everolimus plus octreotide LAR (Pavel et al.).

Compared to advanced small bowel adenocarcinoma, carcinoid tumors carry a better prognosis with 5-year overall survival rates of 68% with resected metastatic disease and 38% with unresectable metastatic disease.

Sarcoma

Epidemiology/Pathology

Small bowel sarcomas account for 8% of all primary small intestinal malignancies and 2% of all sarcomas (Howe et al.). They are often slow-growing tumors with the most common types being leiomyosarcoma and gastrointestinal stromal tumor (GIST), accounting for 75% of small intestine sarcomas. Fibrosarcoma, liposarcoma, and angiosarcoma are less common subtypes.

Based on an NCDB study, 46.8% of small intestinal sarcomas are located in the jejunum, 27.7% in the duodenum, and 25.5% in the ileum. These tumors can spread hematogenously to the liver, lungs, and bone and are capable of invading adjacent tissues.

Risk factors associated with developing small bowel sarcomas are Epstein–Barr virus (EBV), radiation, hereditary retinoblastoma, and Li–Fraumeni syndrome.

Clinical Presentation

Patients typically present with nonspecific abdominal pain (65%), palpable mass (50%), and gastrointestinal bleeding. Because sarcomas in general are slow growing, greater than 75% of lesions are more than 5 cm in size at the time of diagnosis and over half of patients will present with regional

spread or distant metastases.

Cross-sectional imaging will often demonstrate a heterogeneous mass with the presence of necrosis if the tumor has outgrown the blood supply.

Treatment

Surgery with complete resection remains the primary mainstay of therapy for small bowel sarcomas. Unlike small intestine adenocarcinoma and carcinoid tumors, sarcomas rarely metastasize to mesenteric lymph nodes and therefore an extensive lymphadenectomy is not required.

In patients with metastatic disease and complications of bleeding or obstruction, palliative resection or enteric bypass should be considered for symptom control.

Systemic chemotherapy and chemoradiation have a limited role in the treatment of small bowel sarcomas. For leiomyosarcomas, 50% will develop local recurrence and/or distant metastases (Shenoy et al.). Nonsurgical treatment options with chemo or chemoradiation are poor as leiomyosarcomas are rather resistant to radiation therapy and systemic cytotoxic chemotherapies have demonstrated variable response rates with poor improvements in overall survival.

Treatment for localized and metastatic GIST will be discussed separately (Chapter 5).

Lymphoma

Epidemiology/Pathology

The small bowel is the second most common site for primary GI lymphoma following the stomach and accounts for 15% of all primary small intestinal malignancies. GI lymphomas can arise from B or T cells and include Burkitt lymphomas, mucosa-associated lymphoid tissue (MALT) lymphomas, diffuse large B cell lymphomas, and mantle cell lymphomas.

Risk factors associated with developing small bowel lymphomas include Celiac disease, human immunodeficiency virus (HIV), posttransplant lymphoproliferative disorder (PTLD), *Helicobacter pylori*, and immunoproliferative small-intestinal disease (IPSID).

Lymphomas of the small bowel arise from lymphoid tissues, with the greatest density being in the ileum (60% to 65%), followed by the jejunum (20% to 25%), and duodenum (6% to 8%). They are often multifocal with skip lesions present in up to 15% of cases (Nakamura et al.).

Small bowel lymphomas can infiltrate through the mucosa resulting in ulceration and bleeding while enlargement can cause obstruction. Approximately 25% of patients will present with perforation.

Treatment

Patients without symptoms from the small bowel lymphoma should be treated similar to patients with systemic lymphoma and undergo treatment with chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Those that present with complications such as bleeding, obstruction, and perforation often preclude the use of systemic therapy and warrant an operation if comorbidities are not prohibitive. During surgery, the area of the tumor should be resected and careful examination of the remaining small bowel performed to identify potential skip lesions. In contrast to other small bowel tumors, devoted mesenteric resection is not necessary unless it is required to remove the primary tumor. Residual lymph nodes left behind are treated with systemic therapy after the patient recovers.

Chemoradiation can be utilized in patients who are not candidates for cytotoxic chemotherapy. Complications rates with this modality are high from the resultant tumor necrosis, bleeding, and possible bowel perforation.

Metastatic Malignancies

Metastatic lesions to the small bowel are the most common malignancy of the small intestines. These metastases can spread to the small bowel through either hematogenous or lymphatic channels. The primary tumors that often spread to the small intestines arise from the colon, ovary, lung, and melanoma.

Metastases characteristically are found on the surface of the small intestine and can cause bowel obstruction or perforation. Melanoma is unique in that it can spread to the mesenteric lymph nodes and therefore during the time of resection, local lymphadenectomy is recommended.

For metastases from other primaries, resection of the lesion is sufficient without needing to perform a regional lymph node dissection.

Palliation

Metastatic lesions to the small intestine are often bulky and not amendable

to resection. Palliative surgery does however, have a role in these patients. Those that present with small bowel obstruction can be potential candidates for enteric bypass.

In situations of gastrointestinal bleeding, angiography with selective embolization can be considered. However, one major complication of embolization is delayed bowel ischemia and perforation and patients having undergone this procedure should be closely monitored.

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11 Peritoneal Malignancies

Travis E. Grotz, Keith F. Fournier, and Gary N. Mann

INTRODUCTION

Peritoneal carcinomatosis traditionally has been considered a terminal disease. Patients with the condition experience significant suffering from abdominal pain, bloating, and bowel obstruction, and the median overall survival duration from the time of diagnosis is only 5 to 7 months. Until recently, palliative chemotherapy, which increased the median overall survival duration to only 12 months, was the only treatment offered to these patients, because surgery was typically reserved for emergency situations or for the palliation of symptoms. However, a small number of surgeons evaluated the feasibility of surgery for peritoneal malignancies. In 1980, Fernandez and Daly reported on 38 patients with pseudomyxoma peritonei treated at MD Anderson and concluded that the initial treatment for these individuals should be surgical cytoreduction, including omentectomy, appendectomy, and, in female patients, bilateral oophorectomy. That same year, Spratt et al. reported on the successful use of extensive abdominal resection and intraoperative hyperthermic chemotherapy in a patient with pseudomyxoma peritonei. A few years later, Sugarbaker would begin what has become the largest series of cytoreduction and intraperitoneal chemotherapy for peritoneal malignancies.

Surgical resection for oligometastatic disease has long been accepted in malignancies such as melanoma, colorectal cancer, and sarcoma. More recently, peritoneal malignancies are also being approached as a type of regional metastasis in which surgical resection can be performed with curative intent. The observation that many malignancies, such as appendiceal adenocarcinoma, colorectal adenocarcinoma, and peritoneal mesothelioma, remain relatively confined to the peritoneal cavity and infrequently metastasize extra-abdominally, as well as the fact that parietal and visceral peritoneal metastases are relatively superficial, has led to the

investigation of cytoreductive surgery (CRS) as a treatment modality for peritoneal malignancies. The goal of CRS is to systematically evaluate all visceral and parietal peritoneal surfaces and remove all visible disease. However, there is a concern that cytoreduction alone may miss microscopic cells, and that these cells may become entrapped in scar tissue or new tissue planes developed during dissection, leading to early recurrence. For this reason, heated intraperitoneal chemotherapy (HIPEC) is then used to eradicate any microscopic residual disease.

The efficacy of HIPEC depends on several pharmacologic principles, including molecular size, affinity to lipids, first-pass clearance from the plasma by the liver and the permeability of the peritoneal-plasma barrier; optimization of these variables allows for a 10- to 100-fold increased concentration of chemotherapy drug in the peritoneal cavity. High drug concentration within the peritoneal cavity is important, but the drugs must also penetrate tissue to reach invasive cancers growing into the subperitoneal surface. The estimated penetration depth of intraperitoneal chemotherapy is only 3 to 5 mm maximum. Hyperthermia (41° to 42°C) has direct cytotoxic effects and a synergistic effect with chemotherapy, resulting in increased drug penetration of tissue and inhibition of DNA repair mechanisms. Administering intraperitoneal chemotherapy at the time of surgery rather than in the early postoperative period allows for the use of hyperthermia and better distribution of chemotherapy prior to adhesion formation.

HIPEC also has some disadvantages. Adding HIPEC at the time of surgical resection may double the rate of anastomotic leakage and increases the risk of bone marrow suppression, intra-abdominal abscess, and fever. Patients receiving HIPEC at the time of surgery have an average hospital stay of 13 days, an 11% readmission rate, an overall morbidity rate of 33%, and a mortality rate of 2%. Single institutions with high case volumes have reported lower morbidity and mortality rates, suggesting that experience can mitigate some of the adverse events associated with surgeries for peritoneal malignancies. However, these institutions with high case volumes still report significant morbidity and measurable mortality rates. Both the individual and institutional learning curves are steep, with studies reporting that 33 to 70 cases are needed to decrease morbidity rates and 140 to 220 cases are needed to improve the completeness of cytoreduction (CCR).

In order to obtain complete cytoreduction, all visible disease must be

removed, often requiring multiple organ resections, leading to significant morbidity and decreased quality of life (QOL). The most common postoperative complications after CRS and HIPEC are intra-abdominal abscess, gastric or small intestinal perforation, postoperative ileus, anastomotic leakage, postoperative bleeding, fistula, sepsis, respiratory distress, hematologic toxicity, and urinary disturbance. The most common causes of death include anastomotic leakage, sepsis, and postoperative bleeding.

There are several toxicities associated with specific intraperitoneal chemotherapy agents. Bone marrow toxicity occurs in 39% of patients receiving intraperitoneal mitomycin C (dosage: 20 mg/m^2 in patients who received previous systemic chemotherapy and 25 mg/m^2 for chemo-naïve patients); nadirs in absolute neutrophil count typically occur around postoperative day 9, last for 2 days, however this is not associated with increased mortality, infection, or length of hospital stay. Cisplatin (dosage: 200 mg/m^2) is associated with renal toxicity, and renal protective measures are employed when the drug is used (discussed later). Lastly, oxaliplatin (dosage: 200 to 460 mg/m^2) is commonly used for carcinomatosis from colorectal cancer. Oxaliplatin has been associated with unexplained peritoneal bleeding and hepatic dysfunction in phase 1 trials. Moreover, oxaliplatin is unstable in chloride-containing media, necessitating the use of 5% dextrose as the carrier solution. Prolonged peritoneal exposure to this hypotonic solution can cause serious hyperglycemias, electrolyte disturbances, and death. However, recent pharmacologic studies have demonstrated that the more physiologic, chloride-containing carrier solutions, such as plasmalyte, can be used safely with oxaliplatin. In fact, chloride seems to enhance the activity and cytotoxicity of oxaliplatin.

QOL is dramatically reduced postoperatively in patients undergoing CRS and HIPEC, although it appears to return to baseline by 6 to 12 months. Therefore, care must be taken in selecting patients for CRS and HIPEC. It is imperative to exclude patients at the highest risk for significant morbidity or early recurrence, given that these individuals do not benefit from these treatments. Clinical factors such as advanced age, history of tobacco use, extensive prior surgery, low albumin level, and poor performance status have all been associated with increased rates of morbidity, readmission, reoperation, and mortality. Although multiple factors have been evaluated in an attempt to identify patients at the highest risk for recurrence, the ability to achieve a complete cytoreduction remains

the most important predictor of outcome. Previous studies have reported clinical and radiographic scoring systems that can predict the ability to achieve complete cytoreduction (see later in the chapter).

APPENDICEAL ADENOCARCINOMA

Epidemiology

Appendiceal adenocarcinoma is a unique entity with a broad spectrum of behavior. Although it is rare, its incidence has increased from 0.6 cases per 1,000,000 people in 1973 to 2.8 cases per 1,000,000 people in 2011. This increased incidence is likely due to improvements in detection and recognition of the disease. However, younger patients (age <50 years) are disproportionally affected by this change in incidence, which parallels the rising incidence of early-onset colorectal cancer in the United States during the same time period. Obesity, physical inactivity, and the Western-type diet are commonly cited as potential contributing factors for early-onset colorectal cancer. Given the increased frequency with which colorectal polyps and cancers are diagnosed in patients with appendiceal neoplasms, it is possible that the risk factors for these diseases also influence the incidence of appendiceal neoplasms in young adults. Appendiceal adenocarcinoma may present as appendicitis and is the reason for approximately 0.11% to 0.80% of the 500,000 appendectomies performed annually in the United States. Previously, carcinoid tumors were the most common malignancies of the appendix diagnosed during appendectomy; however, recent studies demonstrate that adenocarcinoma is now the most common malignancy of the appendix. There are three subtypes of appendiceal adenocarcinoma: mucinous (55%), nonmucinous colonic (34%), and adenocarcinoid (11%), which has a mixed morphology. Unlike carcinoid tumors of the appendix, which typically metastasize lymphatogenously and later hematogenously to the liver, appendiceal adenocarcinoma most commonly progresses to peritoneal carcinomatosis with infrequent solid-organ and extra-abdominal metastases.

Clinical Presentation

Male patients are most commonly diagnosed with appendiceal adenocarcinoma at the time of appendectomy for presumed appendicitis (34%) or when mucin is identified in an inguinal hernia sack at the time of

hernia repair (25%). In female patients, the disease is most often misdiagnosed as ovarian cancer (39%), and the correct diagnosis is then made when an oophorectomy is performed. As many as 5% of all patients with appendiceal adenocarcinoma are completely asymptomatic and are diagnosed incidentally after undergoing surgery or radiographic imaging for an unrelated cause. Approximately one-third of all patients present with pseudomyxoma peritonei; a clinical condition characterized by abdominal distension, mucinous ascites, and nausea and vomiting from extensive carcinomatosis.

Appendiceal adenocarcinoma is unique in that it metastasizes predominately through peritoneal seeding after perforation of the tumor. The perforation may be completely asymptomatic. A distinctive feature of mucinous adenocarcinoma is its redistribution phenomenon. The mucin and the cells it contains follow the normal flow of peritoneal fluid and are redistributed in a clockwise manner within the peritoneal cavity to sites of fluid absorption through lymphatic lacunae and lymphoid aggregates. Consequently, the tumor tends to spare mobile loops of small intestine early on in the disease process and to first accumulate in other sites such as the pelvis, paracolic gutters, omentum, liver capsule, and right hemidiaphragm. Bulky accumulations can develop as mucin is absorbed at the lymphatic lacunae and epithelial cells are “filtered out” and concentrated into sheets of tumor. Only late in the disease process do mucinous implants develop on the bowel, eventually leading to obstruction. Therefore, malignant bowel obstructions from appendiceal adenocarcinoma are a late finding associated with a decreased probability of complete cytoreduction and decreased survival. Occasionally, mucinous neoplasms from other structures, including the ovary, colon, urachus, and pancreas, may present with the clinical appearance of classic pseudomyxoma peritonei, but the term pseudomyxoma peritonei should be used only to describe the clinical condition of mucinous ascites.

Pathology

Appendiceal adenocarcinoma is also unique in that it is the only malignancy that is classified according to the histologic features of the peritoneal disease rather than the primary tumor. Ronnett et al., in a retrospective review, proposed three prognostic groups based on histologic findings: disseminated peritoneal adenomucinosis (low grade), peritoneal mucinous carcinomatosis (high grade), and peritoneal mucinous

carcinomatosis intermediate (intermediate grade). Subsequent single-institution studies validated the prognostic distinction of the three-tiered staging system suggested by Ronnett et al. However, others have suggested a two-tier system combining the intermediate- and high-grade groups, because of the expected similar outcomes for these two groups. In contrast, a population-based analysis of the National Cancer Database demonstrated significantly different survival outcomes between patients with intermediate-grade and high-grade classifications, suggesting that these two histologic categories should not be classified together, contrary to the recommendations of the seventh edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*. Similarly, a review of 265 consecutive patients with mucinous appendiceal adenocarcinoma treated with CRS and HIPEC at MD Anderson demonstrated significantly different disease-free and overall survival rates among patients with well-differentiated, moderately differentiated, and poorly differentiated appendiceal adenocarcinoma

A consensus statement published in 2008 indicated that 44% of physicians used the Ronnett three-tier classification system, whereas 56% used the two-tier classification system. This problem was discussed at the 2012 World Congress of the Peritoneal Surface Oncology Group International in Berlin, and an updated consensus statement was published in 2016. The expert panel concluded that a two-tier staging system was best and indicated that the terms “low-grade mucinous adenocarcinoma” or “disseminated peritoneal adenomucinosis” were to be used for appendiceal tumors with low-grade histologic features, and the terms “high-grade mucinous adenocarcinoma” or “peritoneal mucinous carcinomatosis” were to be used for appendiceal tumors with high-grade histologic features. A tumor with >50% signet ring cells would be classified as having signet ring cell histology. Appendiceal tumors without infiltrative invasion would be classified as low-grade appendiceal mucinous neoplasms. If no epithelial cells are identified outside the appendix, then the classification “acellular mucin” would be used.

Mucinous histologic features are another important prognostic variable to consider when classifying appendiceal adenocarcinomas. Tumors with mucinous histologic features tend to be well differentiated with scant cellularity and minimal cellular atypia, accompanied by slow, progressive accumulation of mucinous ascites, resulting in the clinical condition of pseudomyxoma peritonei. Patients with mucinous tumors have an

excellent median survival duration of 109 months. In contrast, patients with nonmucinous tumors, which are often moderately or poorly differentiated and characterized by invasive solid peritoneal metastases, have a median survival duration of only 35 months.

Finally, the presence of signet ring cells is a poor prognostic factor for moderately and poorly differentiated tumors. Shetty et al. proposed a classification system that categorized appendiceal adenocarcinoma by grade as low-grade tumors, high-grade tumors without signet ring cells, or high-grade tumors with signet ring cells, with the last group having the poorest prognosis. A review of cases from MD Anderson confirmed that the presence of signet ring cells was an independent predictor of poor survival. Signet ring cells stratified outcome within each histologic grade and therefore represented a complimentary, rather than redundant, prognostic variable.

Staging

In 2010, the AJCC released the seventh edition of its Cancer Staging Manual, which for the first time distinguished appendiceal adenocarcinoma from colorectal adenocarcinoma. In the eighth edition, M1a is now defined as intraperitoneal mucin without identifiable tumor cells, while M1b includes any intraperitoneal metastasis and M1c includes patients with extraperitoneal metastasis. Stage IV is further classified into IVA, IVB, and IVC, depending on lymph node status, tumor grade, and M status. Stage IVA includes patients with intraperitoneal mucin and negative lymph nodes, along with well-differentiated mucinous adenocarcinoma with any lymph node status, whereas stage IVB includes both moderately and poorly differentiated mucinous tumors, irrespective of lymph node status. Stage IVC is any patient with metastases outside the peritoneum. However, the AJCC staging system is infrequently applied in published studies to estimate prognosis; many centers instead report the prognostic significance of mucinous or nonmucinous histologic features, grade, lymph node metastasis, and signet ring cell histologic features. Moreover, the most important independent predictors of outcome remain factors that can be assessed only after surgery, such as the extent of tumor (peritoneal carcinomatosis index [PCI]) and the ability to remove all gross disease (CCR).

The Lyon prognostic index, which was described by Gilly et al. for peritoneal carcinomatosis from gastrointestinal malignancies, takes into

account the size of malignant implants and whether or not the disease is diffuse or localized to one region. The staging system was designed to be applied at time of cytoreduction as well as after cytoreduction and HIPEC. The extent of remaining disease is recorded as the downstaging index resulting from cytoreduction. The stages are as follows: stage 0, no macroscopic disease; stage 1, tumor <5 mm localized to one part of abdomen; stage 2, tumor <5 mm and diffuse to whole abdomen; stage 3, tumor ≥5 mm but ≤2 cm; and stage 4, tumor >2 cm. This staging system is often used by medical oncologists because of its simplicity and reproducibility. It has been used in numerous clinical trials, including EVOCAPE-1, which demonstrated a median survival duration of 6 months for patients with stage 1 or 2 disease compared with a median survival of 3 months for patients with stage 3 or 4 disease.

The PCI, a scoring system created by Sugarbaker, documents the volume and distribution of mucinous implants throughout the abdomen (Fig. 11.1) as determined at the time of operative exploration. After lysis of adhesions and inspection of the entire parietal and visceral peritoneum, the abdomen is divided into 13 regions. Implants within each region are scored as lesion size (LS) 0 through 3. LS-0 means no implants are present throughout the region, LS-1 means implants of up to 0.5 cm are present, LS-2 means implants greater than 0.5 cm and up to 5 cm are present, and LS-3 means that there are implants 5 cm or greater in diameter or that there is a tumor confluence (of any thickness). The PCI is the most commonly reported prognostic scoring system for appendiceal adenocarcinoma and has been correlated with survival. However, several limitations exist. First, the PCI is complex, requiring the surgeon to divide the abdomen into 13 imaginary compartments with no clear anatomic boundaries. In response to this, the Dutch have reported a simplified peritoneal carcinomatosis assessment score in which disease volume is graded as large (>5 cm), moderate (1 to 5 cm), small (<1 cm), or absent in seven abdominal areas: the left and right subdiaphragmatic areas, subhepatic area, omentum/transverse colon, small intestine/mesentery, ileocecal area, and pelvic area. Second, the PCI can be determined only at the time of surgery, limiting its prognostic utility. Determining the PCI on the basis of preoperative imaging is difficult and inaccurate because the extent of disease is often underestimated by imaging. A small series from the Mayo Clinic comparing radiographic and clinical PCI at the time of CRS reported a correlation of 0.59 for appendiceal and 0.62 for colon

adenocarcinoma. Furthermore, 46% of patients with a radiologic PCI score ≥20 were still able to achieve adequate cytoreduction and would have been turned away if a radiographic PCI of 20 was used as a strict criterion for CRS and HIPEC. Therefore, radiographic PCI is helpful in evaluating the volume and distribution of disease, but it offers no definite cut-off values for appendiceal adenocarcinoma that are sensitive and specific enough to warrant patient exclusion from CRS and HIPEC.

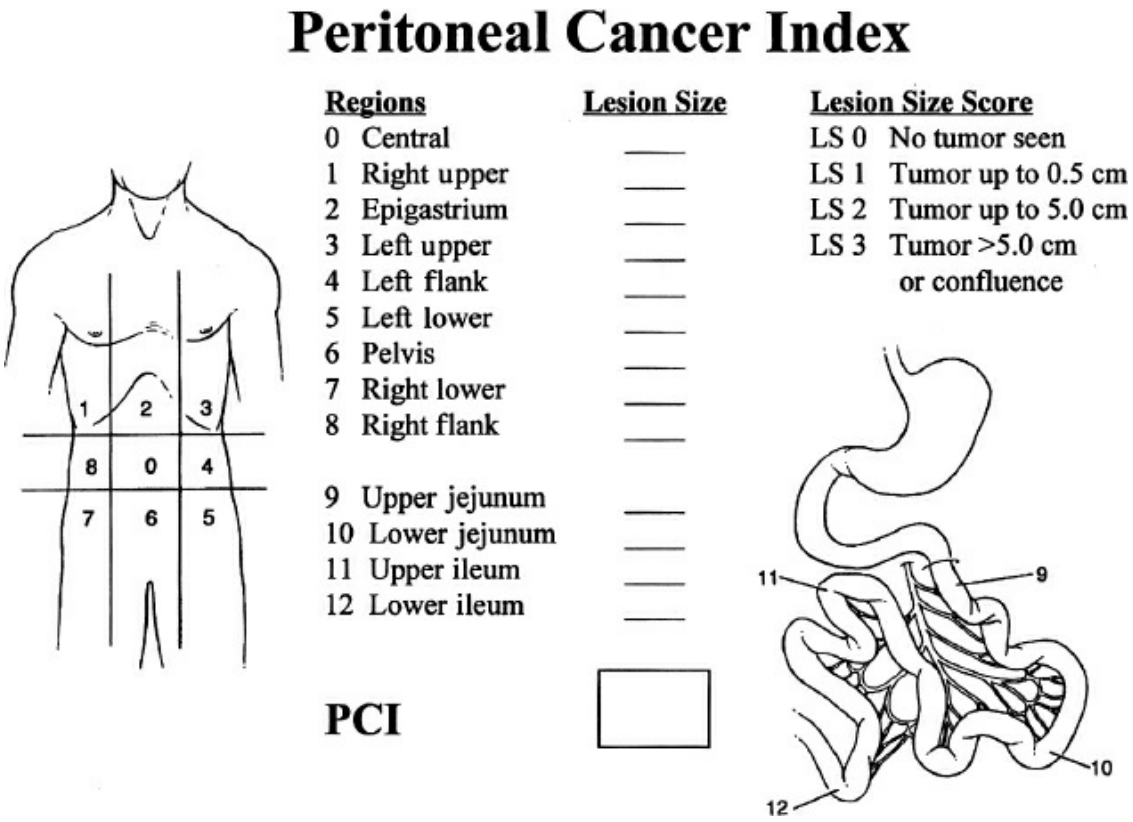

Figure 11.1 Illustration demonstrating how the Peritoneal Carcinomatosis Index (PCI) is obtained. (Used with permission from Carmignani CP, Esquivel J, Sugarbaker PH. Cytoreductive surgery and intraperitoneal chemotherapy for the treatment of peritoneal surface malignancy *Clin Transl Oncol.* 2003;5:192–198.)

Sugarbaker also developed a CCR score that describes the amount of disease remaining after cytoreduction (Fig. 11.2). The scores are as follows: CCR-0, no visible tumor nodules remaining; CCR-1, persistence of tumor nodules <2.5 mm; CCR-2, tumor nodules ≥2.5 mm but ≤2.5 cm; and CCR-3, tumor nodules >2.5 cm. Because hyperthermic intraperitoneal chemotherapy is thought to penetrate to a depth of 2.5 mm, scores of CCR-0 and CCR-1 indicate complete cytoreduction and CCR-2 and CCR-3

indicate incomplete cytoreduction. This scoring system has been consistently demonstrated to be the most important prognostic factor for patients with carcinomatosis of appendiceal origin who undergo CRS and HIPEC.

Given the importance of complete cytoreduction to long-term survival, various scoring systems have been proposed that predict the likelihood of accomplishing complete cytoreduction. One such scoring system for patients with well-differentiated appendiceal adenocarcinoma is the Simplified Preoperative Assessment for Appendix Tumor (SPAAT) scoring system developed at MD Anderson. SPAAT utilizes preoperative computed tomography (CT) studies to grade the volume of disease in five anatomic locations. The presence of scalloping or indentation of the liver, spleen, pancreas, or portal vein from mucinous implants is assessed, and one point is given for each location where scalloping or indentation is present. The bowel is also assessed for involvement, and if the small bowel appears to float to the abdominal wall without evidence of mesenteric foreshortening, it is scored as a 0. Patients with mesenteric foreshortening, which causes the small bowel to appear tethered or cocoon-like on CT images (a condition termed “cauliflowering” of the bowel), are given a score of 3. SPAAT scores range from 0 to 7, and a score of ≥3 has 100% sensitivity and 93% specificity with 95% positive predictive value for identifying patients in whom a complete cytoreduction will not be obtainable. These patients are not offered CRS and HIPEC because the median overall survival for patients with a SPAAT ≥3 was found to be only 10 months. The exception to this recommendation is the symptomatic patient with minimal comorbidities and preserved nutritional and functional status. In these patients, we offer an organ-sparing, incomplete debulking in which the omentum is resected to improve the symptoms of ascites and we address potential sources of bowel obstruction. The patients also receive HIPEC for a shorter duration than is normally used (30 minutes instead of 90 minutes) because there are numerous reports of improvement in malignant ascites after palliative HIPEC.

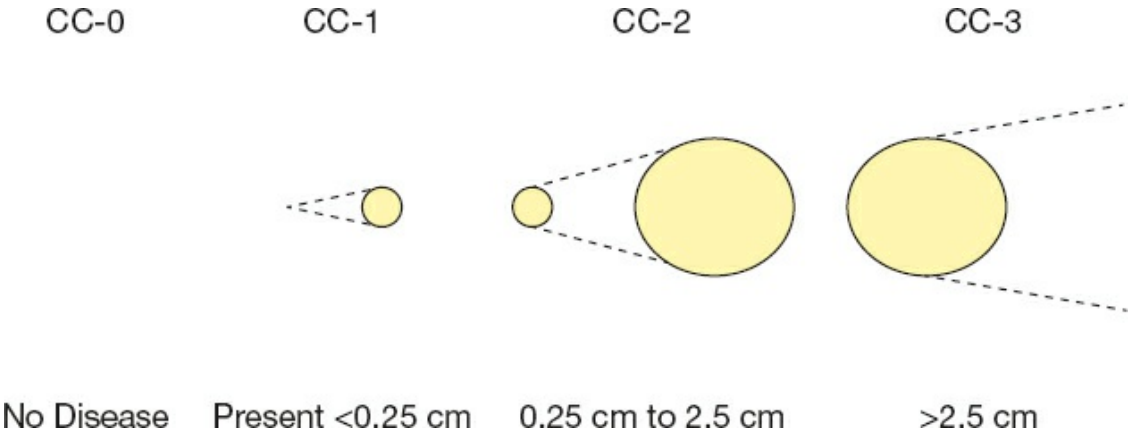

Figure 11.2 Illustration of the completeness of cytoreduction (CCR) Score that is calculated after completing cytoreduction. (Used with permission Sugarbaker P. *Management of Peritoneal Surface Malignancy Using Intraperitoneal Chemotherapy and Cytoreductive Surgery.* 3rd ed.)

Diagnostic Workup

Histologic confirmation of appendiceal adenocarcinoma is often obtained at the time of incidental appendectomy or oophorectomy for presumed ovarian cancer. The pathologic report should be read by an experienced gastrointestinal pathologist at a center familiar with peritoneal malignancies. The operative report for the index operation should be carefully reviewed for details regarding the extent of disease. If appendiceal adenocarcinoma is encountered unexpectedly at the time of an unrelated operation, the recommendation is to perform limited resection to confirm the histologic diagnosis and document the extent of disease without performing unnecessary dissection. The rationale for this is that one of the important predictors of morbidity and of the ability to obtain a complete cytoreduction is the previous surgical score (PSS). The PSS takes into account the extent of any surgeries prior to the definitive CRS and HIPEC. The more extensive the previous surgery, the more morbidity is expected, and the smaller the likelihood of obtaining a complete cytoreduction. PSS scores are as follows: PSS-0, no previous surgery or biopsy only; PSS-1, previous surgery involving only one region; PSS-2, two to five regions previously dissected; and PSS-3, previous attempt at CRS and HIPEC. Patients scoring PSS-2 or PSS-3, that is, those who have had extensive prior surgery, are less likely to have a complete cytoreduction because unnecessary dissection entraps residual tumor cells in scar tissue. Extensive adhesions not only increase the morbidity of

subsequent operations but also make it difficult to distinguish between tumor implants. In addition, local growth factors after surgery may promote the growth of residual cells. Therefore, partial debulking surgery at the time of incidental diagnosis is strongly discouraged because it is not beneficial to patients, delays definitive treatment, and hinders the chances of a complete cytoreduction later.

If no histologic diagnosis has been obtained and a patient is diagnosed incidentally through imaging, then some imaging characteristics can be used to help make a diagnosis. Calcification of the appendix is a specific but not a sensitive indicator of appendiceal adenocarcinoma; less than 50% of patients will have this finding. An appendix with a diameter >15 mm and a soft-tissue mass or wall thickening, or a finding of mucin outside of the appendix, is highly suspicious for an appendiceal adenocarcinoma. Mucin can be observed as free-floating ascites, or it can be encapsulated in a cystic manner often with mural calcifications. A percutaneous biopsy of the densest nodularity, which is usually found in the omentum, should be performed. Difficulty aspirating fluid during paracentesis is also suggestive of the thick mucin associated with mucinous appendiceal adenocarcinoma.

Once a histologic diagnosis has been confirmed with a biopsy or previous resection, the extent of disease must be assessed by high-quality imaging of the abdomen and pelvis in the form of multidetector CT with enteric and parenteral contrast reconstructed to <5 mm axial, sagittal and coronal planes or magnetic resonance imaging (MRI) with diffusion-weighted imaging and intravenous gadolinium contrast. CT studies are most commonly used, are routinely available, and are the imaging modality of choice at MD Anderson. However, because CT does not detect disease <5 mm, underestimation of the PCI is possible. Other institutions have reported that preoperative PCI scores established through gadolinium-enhanced MRI correlate better with PCI scores established through surgery than do preoperative PCI scores established through CT and that gadolinium-enhanced MRI offers notable improvements in the detection of small bowel nodules. Regardless of the imaging modality of choice, having the scan interpreted by an experienced radiologist is critical because peritoneal disease is often subtle on imaging and requires a high index of suspicion.

A preoperative colonoscopy is highly recommended because there is a higher incidence of colonic polyps and invasive adenocarcinoma in

patients with appendiceal adenocarcinoma. Synchronous colon polyps have been reported in 42% of patients and metachronous colonic cancers in 5% to 21%. The use of colonoscopy for diagnosis of appendiceal adenocarcinoma is inappropriate because only 11% of patients in the largest series of preoperative colonoscopies for appendiceal adenocarcinoma had abnormal appendiceal findings.

Preoperative evaluation of the patient's candidacy for CRS and HIPEC includes a complete history and a physical examination detailing comorbidities and functional status. Obtaining a social history is also important because smoking is a significant independent predictor of morbidity. Smoking cessation should be highly encouraged. Patients must have preserved renal, hepatic, and cardiac function to tolerate the effects of a long operation with significant fluid shifts. Medications must be reviewed to ensure cessation of any anticoagulants prior to surgery. Nutritional status can be assessed with body mass index, recent weight changes, body habitus, and albumin and prealbumin levels. At MD Anderson, the patients considered to be the best candidates for CRS and HIPEC are <70 years old, do not smoke, have an Eastern Cooperative Oncology Group (ECOG) functional status of 0 or 1, and have maintained their nutritional reserves (albumin >3.5 g/dL).

The tumor marker, CEA, is elevated in 56% of patients with appendiceal adenocarcinoma and CA 19-9 is elevated in 67%. However, serum CEA and CA 19-9 levels are not useful for diagnosis of appendiceal adenocarcinoma because they lack sensitivity and specificity. Although the absolute level of a tumor marker does not correlate with prognosis, a normal value is associated with improved survival outcomes. Furthermore, elevated preoperative levels of CEA or CA 19-9 should return to baseline within 7 days after complete resection, and residual disease should be suspected if these levels do not return to baseline. We suggest obtaining serum CEA and CA 19-9 levels at each follow-up visit for at least the first 5 years after CRS and HIPEC, even if preoperative levels were normal, as long as the patient would be considered a candidate for further aggressive therapy, including surgery. Carmignani et al. reported elevated serum CEA levels in 35% of 110 patients determined to have recurrent disease during surveillance. In addition, CA 19-9 was elevated in 63% of patients, and at least one of the tumor markers was elevated in 68% of patients. An elevated CEA level at the time of recurrence indicated a poorer prognosis. Studies in colorectal cancer suggest that elevation of tumor markers

precedes findings on imaging by 1.5 to 6 months.

Well-Differentiated Mucinous Appendiceal Adenocarcinoma (Low-grade)

Our algorithm for treating well-differentiated, mucinous appendiceal adenocarcinoma is shown in Figure 11.3. Patients with localized disease have often had a previous laparoscopic appendectomy prior to referral to MD Anderson. Postoperatively, if imaging shows no evidence of residual disease, the tumor markers are normal, the margins on the appendiceal base are negative, and the colonoscopy is normal, then we would not recommend performing a right hemicolectomy because the incidence of nodal metastasis for well-differentiated mucinous appendiceal adenocarcinoma is <5%. Instead, we would recommend surveillance every 6 months with a history and physical examination, CT imaging, and determination of tumor marker levels every 6 months for the first 2 years and then annually thereafter.

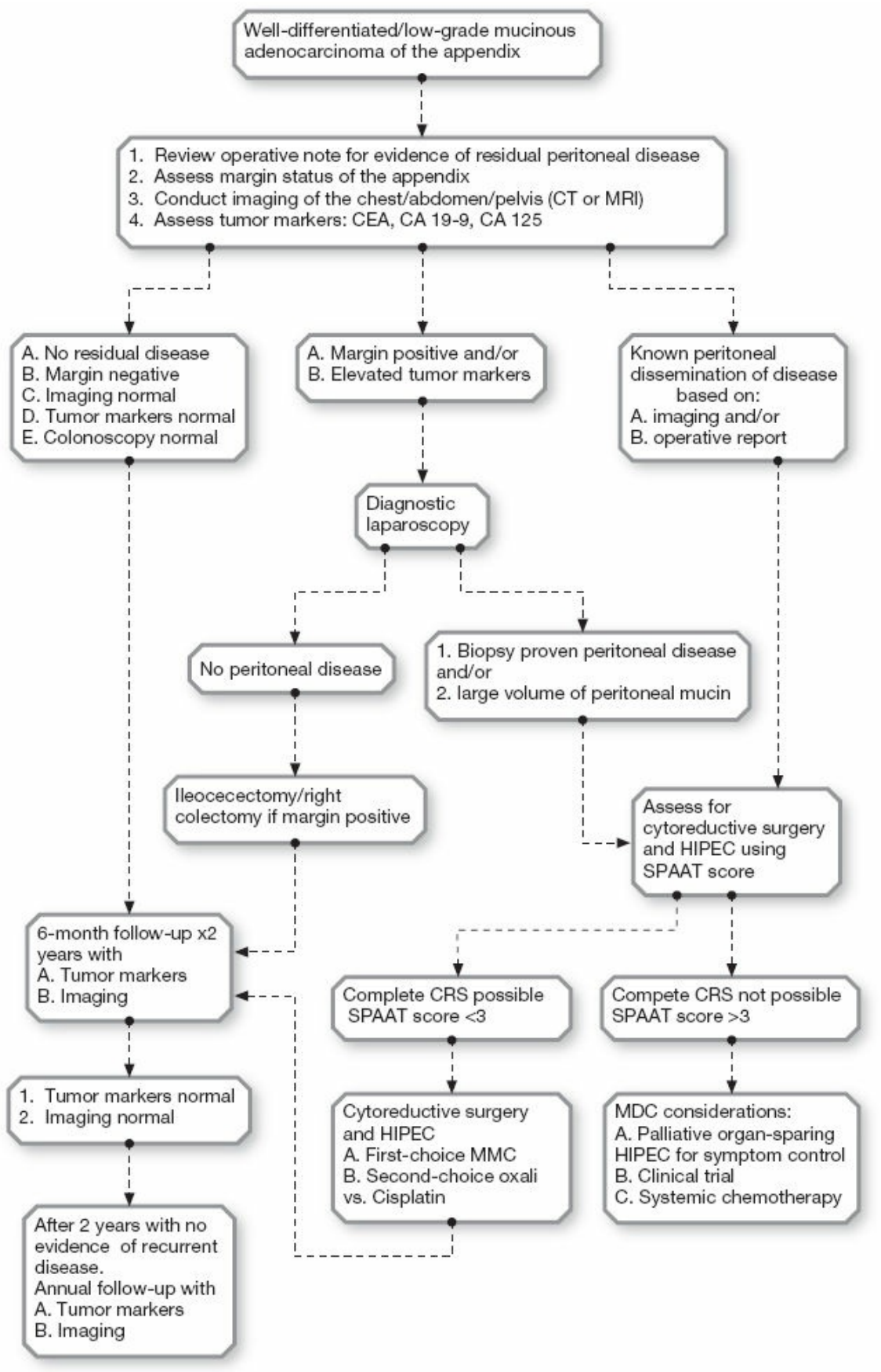

Figure 11.3 Algorithm for the multidisciplinary management of well-differentiated mucinous appendiceal adenocarcinoma.

If a patient has residual disease on baseline imaging, we recommend determining the patient's SPAAT score to determine whether complete cytoreduction is possible. If a patient's medical comorbidities, nutritional status, and functional status permit, we then offer potentially curative CRS and HIPEC to a patient with a SPAAT score <3. We typically wait 3 to 4 months from the last operation to allow inflammation to resolve. A right hemicolectomy is recommended only for patients with well-differentiated tumors with positive appendiceal base margins or with visible serosal disease. For patients with a SPAAT score ≥3 who are symptomatic but have manageable comorbidities and preserved functional and nutritional status, we offer palliative, organ-preserving debulking and HIPEC. This approach attempts to balance morbidity and tumor debulking. For patients with unresectable well-differentiated mucinous appendiceal adenocarcinoma we do not recommend palliative chemotherapy because there has been no demonstrable benefit to systemic chemotherapy in these patients. These individuals are best managed with supportive care or a clinical trial.

Well-differentiated tumors have an indolent course with slow progression; the median time to recurrence is 22 months. Therefore, for patients with these tumors, we recommend surveillance consisting of a history and physical examination, testing for serial tumor markers (CEA, CA 19-9, and CA 125), and serial imaging of the abdomen and pelvis every 6 months for 2 to 3 years and then annually thereafter. There is no clear time interval when there is no risk of recurrence; therefore, we follow patients until they feel comfortable following up with their primary care physicians for a history and physical examination alone. Our longest interval recurrence for well-differentiated tumors was 100 months. Also, given the slow progression of the disease, new findings on imaging can be followed for clinical behavior to help distinguish recurrent tumors from residual acellular mucin or scars.

Moderately and Poorly Differentiated Appendiceal Adenocarcinoma (Intermediate- and High-Grade)

Our algorithm for treating moderately and poorly differentiated appendiceal adenocarcinoma is shown in Figure 11.4. Briefly, patients with localized disease often have had a previous laparoscopic appendectomy at an outside institution prior to referral to MD Anderson. If no evidence of residual disease is seen on postoperative imaging and

tumor markers are not elevated, we recommend performing a diagnostic laparoscopy and if no peritoneal disease is present then we would proceed with a right hemicolectomy to assess lymph node metastasis because the risk of lymph node metastasis approaches 44% in this cohort. If the ileocolic lymph nodes are positive, we recommend adjuvant systemic chemotherapy because lymph node metastases are associated with poor 5-year overall survival rates (33% compared with 74% for patients without lymph node involvement). If no peritoneal disease is evident on laparoscopic exploration and the ileocolic lymph nodes are negative, then we recommend surveillance with follow-up. Follow-up should include a history and physical examination, CT imaging of the chest, abdomen, and pelvis, and testing for tumor markers every 3 to 4 months for the first 2 to 3 years. Follow-up can then be done every 6 months until the 5-year mark is reached and can thereafter be done annually.

If the patient has radiographic evidence of peritoneal disease then we recommend careful evaluation of the CT scan for evidence of small bowel mesenteric involvement (cauliflowering of the bowel) or porta hepatis involvement; these are the two most difficult areas from which to surgically clear disease. In general, a PCI score <20 is considered more favorable for a complete cytoreduction, and improved overall survival. However, we do not use this as an absolute cut-off because select patients with a PCI score ≥20 have meaningful, long-term survival. We recommend that all patients receive neoadjuvant systemic chemotherapy, preferably folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or folinic acid, fluorouracil, and irinotecan hydrochloride (FOLFIRI) with bevacizumab, for four to six cycles. Potential benefits of the neoadjuvant approach include better tolerance of chemotherapy and, as a result, an increased likelihood of completing the intended therapy. Preoperative therapy also facilitates the assessment of tumor biology and chemosensitivity. Modern chemotherapy regimens with FOLFOX or FOLFIRI and bevacizumab have radiographic response rates of 38% to 50%, which corresponds to an improved median disease-free survival duration of 27 months and median overall survival duration of 48 months. Patients who are not candidates for surgical resection also have improved rates of progression-free and overall survival when receiving this type of chemotherapy regimen. A lack of response may indicate that the patient will not benefit from CRS and HIPEC, because patients who do not respond to FOLFOX or FOLFIRI and bevacizumab have a median

disease-free survival duration of only 14 months and a median overall survival duration of 22 months. A lack of response may also indicate a need to change the chemotherapy regimen to one that potentially will induce more of a clinical, biochemical, or radiologic response. We have demonstrated that neoadjuvant systemic chemotherapy had no detrimental effects on blood loss, operative time, hospital length of stay or morbidity provided the bevacizumab is completed 8 weeks prior to CRS and HIPEC.

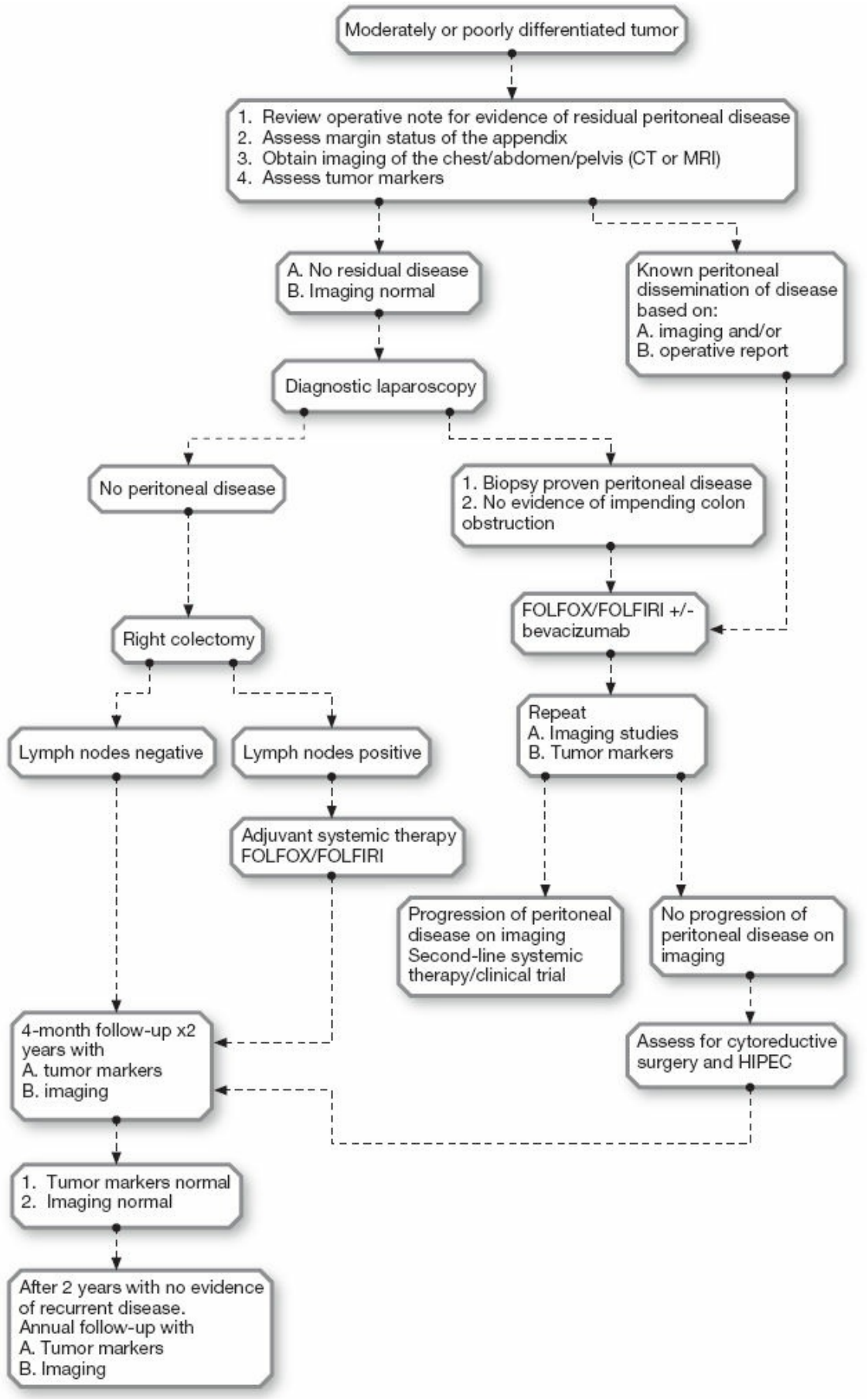
Moderately or poorly differentiated tumor
1. Review operative note for evidence of residual peritoneal disease
2. Assess margin status of the appendix
3. Obtain imaging of the chest/abdomen/pelvis (CT or MRI)
4. Assess tumor markers
A. No residual disease
B. Imaging normal
Known peritoneal dissemination of disease based on:
A. imaging and/or
B. operative report
Diagnostic laparoscopy
No peritoneal disease
1. Biopsy proven peritoneal disease
2. No evidence of impending colon obstruction
FOLFOX/FOLFIRI +/- bevacizumab
Right colectomy
Repeat
A. Imaging studies
B. Tumor markers
Lymph nodes negative
Lymph nodes positive
Adjuvant systemic therapy FOLFOX/FOLFIRI
Progression of peritoneal disease on imaging
Second-line systemic therapy/clinical trial
No progression of peritoneal disease on imaging
4-month follow-up x2 years with
A. tumor markers
B. imaging
Assess for cytoreductive surgery and HIPEC
1. Tumor markers normal
2. Imaging normal
After 2 years with no evidence of recurrent disease.
Annual follow-up with
A. Tumor markers
B. Imaging

Figure 11.4 Algorithm for the multidisciplinary management of moderately and poorly differentiated appendiceal adenocarcinoma.

After patients recover from neoadjuvant chemotherapy, we offer them a diagnostic laparoscopy, if possible, to determine if the extent and volume of disease is amenable to cytoreduction, given that CT studies consistently underestimate PCI. Diagnostic laparoscopy has been demonstrated to be a safe and feasible adjunct to preoperative imaging in the vast majority of patients. We have found it to be particularly useful in identifying small bowel and mesenteric metastases, which are often missed on imaging. The current literature suggests that a high percentage (20% to 44%) of patients undergo incomplete cytoreduction in the absence of preoperative laparoscopy. In one study, the use of diagnostic laparoscopy spared half of patients a nontherapeutic laparotomy and its associated morbidity. With the judicious use of diagnostic laparoscopy, we have been able to reduce our rate of incomplete cytoreduction to <10%.

Moderately and poorly differentiated tumors usually follow an aggressive course and can recur rapidly (median time to recurrence: 16 months). Therefore, we recommend close surveillance for affected patients. Surveillance consists of a history and physical examination, an assessment of serial tumor markers (CEA, CA 19-9, and CA 125), and serial imaging of the chest, abdomen, and pelvis every 3 to 4 months for 2 years. Patients then receive surveillance every 6 months until the 5-year mark and annually thereafter. Our longest interval to recurrence was 74 months for a moderately differentiated tumor.

Outcomes

An improvement in survival for appendiceal neoplasms was observed from 1973 to 2006 mainly owing to better survival in patients with advanced disease. Major advances in the management of advanced appendiceal neoplasms during this period led to the recognition of the benefit of complete surgical cytoreduction and the introduction of HIPEC in the 1980s.

A recent review of 265 patients with mucinous appendiceal adenocarcinoma treated with CRS and HIPEC at MD Anderson demonstrated 5-year overall survival rates of 94% for patients with well-differentiated tumors, 71% for moderately differentiated tumors, and 30%

for patients with poorly differentiated tumors. The corresponding 5-year disease-free survival rates were 66%, 21%, and 0%. If acellular mucin alone was found outside the appendix at the time of CRS and HIPEC in a patient with well-differentiated appendiceal adenocarcinoma, then the prognosis was excellent; all such patients remained alive without evidence of disease after a median follow-up of 54 months. Other independent predictors of improved survival included mucinous histology, lower histologic grade, lower PCI score, and complete cytoreduction. Patients with mucinous tumors had a median overall survival duration of 109 months. Those with nonmucinous tumors did significantly worse with a median overall survival duration of only 36 months.

Approximately 40% of patients with appendiceal adenocarcinoma develop a recurrence after complete CRS and HIPEC. More than half of these patients are candidates for repeat CRS and HIPEC, and a second complete cytoreduction is achieved in most of them. Patients who undergo a repeat CRS with or without HIPEC have improved survival outcomes compared with those who do not undergo repeat CRS and HIPEC, and this is true even after controlling for clinical and pathologic factors. Patients are carefully selected for repeat CRS and HIPEC. The morbidity (37%) and mortality (0%) rates for repeat cytoreduction and HIPEC are similar to those for primary CRS and HIPEC (55% and 0.8%, respectively). Some clinicians have found that early recurrence within 12 months of a complete cytoreduction is an indicator of a poor prognosis, associated with a median overall survival duration of 38 months. In contrast, patients who remain disease-free for more than 12 months have a more favorable prognosis and are candidates for repeat CRS and HIPEC, frequently with an alternative chemotherapeutic agent; they also have a median overall survival duration of 97 months. Data from MD Anderson have shown that patients with preserved functional status, absence of signet ring cells, absence of distant metastasis, low PCI and those able to undergo complete cytoreduction may have the most pronounce benefit from repeat CRS +/– HIPEC

PERITONEAL CARCINOMATOSIS IN PATIENTS WITH COLORECTAL CANCER

Incidence and Risk Factors

A Swedish population study demonstrated that approximately 8.3% of patients with colorectal cancer will also have synchronous or

metachronous peritoneal carcinomatosis. Peritoneal carcinomatosis was the first and only type of metastasis in 4.8% of patients. The prevalence of synchronous peritoneal carcinomatosis was 4.3%, and the cumulative incidence of metachronous peritoneal carcinomatosis was 4.2%. Each year, there are an estimated 95,270 new patients with colon cancer and 39,220 new patients with rectal cancer in the United States. Of these, approximately 6,455 patients have peritoneal carcinomatosis and might be candidates for CRS and HIPEC.

Independent predictors of metachronous peritoneal carcinomatosis are right-sided colon cancer, primary stage T4 tumors, advanced nodal status, emergency surgery, and nonradical resection of the primary tumor. Patients older than 70 years have a decreased risk of metachronous peritoneal carcinomatosis.

Staging

The colorectal cancer section in the eighth edition of the AJCC Cancer Staging Manual classifies any metastasis to the peritoneal surface as stage IVC. However, distinct survival differences between stage IVA (metastasis to a single organ, excluding the peritoneum), stage IVB (metastasis to multiple organs, excluding the peritoneum), and stage IVC (peritoneal surface metastases), have not been published. As is the case with appendiceal adenocarcinoma, the Lyon and PCI staging systems are important for staging peritoneal carcinomatosis of colorectal origin. The SPAAT score was intended for low-grade appendiceal adenocarcinoma and has not been evaluated for peritoneal carcinomatosis from colorectal cancer. Instead, the Peritoneal Surface Disease Severity Score (PSDSS) was recently introduced as a means of categorizing patients with colorectal peritoneal carcinomatosis into prognostic groups to improve patient selection. The PSDSS takes into account symptoms, the extent of carcinomatosis, and primary tumor histologic features to assign a score of between 2 and 22 points. Stage I is defined as <4 points, stage II as 4 to 7 points, stage III as 8 to 10 points, and stage IV as >10 points. In a validation cohort of 1,013 patients with peritoneal carcinomatosis of colorectal origin, the median overall survival duration was 86 months for stage I, 43 months for stage II, 29 months for stage III, and 28 months for stage IV. Several studies have demonstrated that the PSDSS is an independent prognostic factor, and it has proven to be better than the PCI in stratifying overall survival and progression-free survival. Another group

externally validated the PSDSS but suggested modifying the nomogram to include four important prognostic factors; age, PCI score, locoregional lymph node status, and signet ring cell histologic features. The resultant precytoreduction nomogram, which has been termed the colorectal peritoneal metastases prognostic surgical score (COMPASS), is more accurate than the PSDSS in predicting overall survival of patients undergoing CRS with HIPEC, has not been externally validated. Therefore, the PCI and PSDSS remain the most commonly used staging/scoring systems for peritoneal carcinomatosis of colorectal origin.

Treatment

National Comprehensive Cancer Network (NCCN) guidelines recommend complete cytoreduction and/or intraperitoneal chemotherapy at experienced centers for select patients with limited peritoneal metastasis for whom an R0 resection can be achieved. Long-term outcomes after CRS and HIPEC for colorectal peritoneal carcinomatosis depend on the volume and distribution of peritoneal spread as measured by the PCI. Therefore, to improve the probability of a complete cytoreduction and long-term survival, it is important to diagnose and treat peritoneal recurrences early. Population-based studies suggest that patients with T4a primary tumors, N1 or N2 node status, mucinous histologic features, and a history of incomplete or emergency resection are at the highest risk of peritoneal relapse. Between 18% and 50% of patients with a T4 primary tumor develop peritoneal carcinomatosis as a result of the intra-abdominal exfoliation of cancer cells that had invaded the entire thickness of the colon wall and its investing serosa. One-quarter of these relapses will be isolated peritoneal recurrences.

Currently, close surveillance with serial imaging and intervention if radiographic recurrent disease is identified is the standard for patients at risk for peritoneal recurrence. However, diagnostic imaging is currently insufficient for the identification of early peritoneal disease, which is most likely to respond to CRS and HIPEC. Therefore two other approaches are currently being investigated. One approach is to perform second-look surgery in patients with no radiographic evidence of disease at the end of a fixed time interval after initial treatment. A French study evaluating this approach in 29 patients with high-risk features (minimal synchronous macroscopic peritoneal disease, synchronous ovarian metastasis, or perforation) revealed asymptomatic, radiographically occult peritoneal

disease in 56% of patients 1 year after resection of their primary tumors. These patients were then treated with CRS and HIPEC and had an excellent 5-year overall survival rate of 90%. Unfortunately, a prospective trial that randomized patients with CRC who were at high risk for developing peritoneal carcinomatosis to mandatory second-look surgery or standard-of-care surveillance was withdrawn prior to accrual. The second approach, in an effort to prevent peritoneal recurrence, is to offer prophylactic HIPEC to patients with risk factors for peritoneal recurrence but no evidence of peritoneal disease. A prospective study of 25 patients with risk factors for peritoneal spread (pT3/pT4 and mucinous or signet ring cell histologic features) reported local and peritoneal recurrence in only 4% of patients after prophylactic HIPEC compared with 28% in matched controls. The median disease-free survival duration in these patients was also significantly better than in matched controls (36.8 months compared with 21.9 months). However, evidence in support of prophylactic HIPEC remains limited to small series that used varying selection criteria, confounding the interpretation of the results. Therefore, second-look surgery and/or prophylactic HIPEC cannot be recommended outside of a clinical trial.

Our algorithm for treating peritoneal metastasis from colorectal cancer is similar to the algorithm for moderately and poorly differentiated appendiceal adenocarcinoma shown in Figure 11.4. Patients with synchronous or metachronous peritoneal carcinomatosis from colorectal cancer undergo a similar evaluation to that done for patients with appendiceal adenocarcinoma; the evaluation includes a detailed history and physical examination detailing comorbidities, and functional and nutritional status. If a colonoscopy had not been done recently, one is performed to evaluate for synchronous colon cancers or polyps. High-quality imaging of the chest, abdomen, and pelvis is performed to exclude other sites of metastatic disease and to determine the radiographic PCI score. A PCI score of >17 is considered a relative contraindication to CRS and HIPEC; Goere et al. demonstrated that patients with peritoneal carcinomatosis of colorectal origin and a PCI score >17 who undergo CRS and HIPEC have a similar survival rate to those patients who undergo palliative operations only. Our algorithm differs from the consensus algorithm published by Esquivel in 2007 in that we routinely recommend neoadjuvant systemic chemotherapy with bevacizumab in all patients with colorectal peritoneal carcinomatosis. Data since Esquivel’s publication

now demonstrates that neoadjuvant systemic chemotherapy with bevacizumab is an independent predictor of improved OS. Therefore, we recommend that all patients undergo neoadjuvant systemic chemotherapy with FOLOFOX or FOLFIRI with bevacizumab for four to six cycles and that they then be reassessed for response. We then recommend diagnostic laparoscopy for all patients who have stable or responsive disease according to the restaging imaging studies. The intent of the diagnostic laparoscopy is to get a more accurate PCI score and to evaluate the involvement of the bowel and portal structures because these are the most difficult areas to clear free from disease. We offer CRS and HIPEC to patients who have limited comorbidities, preserved nutritional and functional status, a PCI score <17, and no extensive bowel involvement.

Consensus guidelines from the American Society of Peritoneal Surface Malignancies recommend the closed technique with the administration of mitomycin C 30 mg at time zero and an additional 10 mg (for a total of 40 mg) at 60 minutes in a total of 3 L for a 90-minute perfusion. The goal inflow temperature is 42°C. This is widely practiced around the world. At MDACC we typically use mitomycin C (dosage: 20 mg/m^2 in patients who received previous systemic chemotherapy and 25 mg/m^2 for chemo-naïve patients) at time zero for a 90 minute perfusion with similar other parameters. Two retrospective studies suggest improved overall survival outcomes in the colorectal patients receiving intraperitoneal perfusion with oxaliplatin. However, the largest multicenter evaluation by the American Society of Peritoneal Malignancies demonstrated improved OS for those patients with PSDSS I and II with mitomycin C and a nonsignificant improvement in overall survival for those with PSDSS III and IV receiving Oxaliplatin. Therefore, the optimal perfusion agent for peritoneal carcinomatosis from CRC remains to be determined.

Outcomes

A study in the Netherlands by Verwaal et al. randomized 105 patients to receive either (1) standard treatment consisting of systemic chemotherapy (5-fluorouracil and leucovorin) with or without palliative surgery, or (2) cytoreduction with HIPEC, followed by the same systemic chemotherapy regimen. The trial demonstrated a near twofold increase in median overall survival for patients who received CRS and HIPEC compared with those who received systemic chemotherapy only (22 months compared with 12 months). Furthermore, patients who had a complete cytoreduction

achieved a 5-year overall survival rate of 45%. Critics of this study cite the use of 5-fluorouracil and leucovorin as an inadequate and rarely used chemotherapy regimen and suggest that median overall survival is improved with the use of newer chemotherapy regimens with oxaliplatin, irinotecan, and bevacizumab. However, a pooled analysis of 2,095 patients enrolled in two prospective randomized trials of oxaliplatin and irinotecan demonstrated that peritoneal carcinomatosis from colorectal cancer is associated with a significantly shorter median overall survival (duration of 12 months) and progression-free survival (duration of 6 months) compared to patients with other manifestations of metastatic colorectal cancer. Subsequent single-institution studies have demonstrated that overall survival following CRS and HIPEC in patients with peritoneal carcinomatosis from colorectal cancer is similar to that of patients undergoing hepatic resection for colorectal liver metastasis. Some centers have reported 5-year overall survival rates exceeding 50%.

A consensus statement published in 2007 recommended the use of CRS and HIPEC for carefully selected patients with peritoneal carcinomatosis of colorectal origin. The ability to obtain a complete cytoreduction is the most predictive factor of long-term survival in these individuals. Variables associated with a complete cytoreduction include:

1. Preserved ECOG performance status (≤2)
2. No evidence of extra-abdominal disease
3. No more than three small, resectable hepatic metastases
4. No evidence of biliary obstruction
5. No evidence of ureteral obstruction
6. No evidence of intestinal obstruction at more than one site
7. Small bowel involvement: no gross small bowel mesenteric involvement causing segmental partial bowel obstruction
8. Small-volume disease in the gastrohepatic ligament

Most of the literature on outcomes for CRS and HIPEC in patients with peritoneal carcinomatosis report a median survival of 32 to 47 months. However, even with careful patient selection and complete cytoreduction, disease recurrence occurs in 48% to 70% of patients at a median interval of 12 months. Between 31% and 57% of these patients present with isolated peritoneal recurrence. Several retrospective studies suggest that 12% to 36% of patients with peritoneal recurrences may be candidates for repeat CRS and HIPEC. Again, these patients must be carefully selected; CCR and a low tumor burden are the predominant predictors of improved

survival. Morbidity and mortality for repeat CRS and HIPEC has been demonstrated to be similar to the first CRS and HIPEC. Given the importance of obtaining a complete cytoreduction on the second CRS and HIPEC and the potential for significant morbidity, we strongly caution against repeat CRS and HIPEC in patients with diffuse intra-abdominal recurrence because these patients have much poorer long-term survival outcomes.

MALIGNANT PERITONEAL MESOTHELIOMA

Epidemiology

Mesothelioma is a rare malignancy affecting the cuboidal cells lining the pleura (75% of cases), peritoneum (20%), pericardium (5%), or tunica vaginalis (<1%). The disease is regarded as universally fatal and is poorly understood. Exposure to asbestos increases the risk of mesothelioma after a latency period of 20 to 40 years, but although asbestos is the environmental factor most commonly associated with mesothelioma, it does not transform human mesothelial cells in tissue culture. This indicates that additional carcinogens act in conjunction with asbestos to cause mesothelioma. Recent evidence suggests that simian virus 40, a polyomavirus that can transform hamster mesothelial cells, acts with asbestos to produce mesothelioma in several independent animal models and human cell lines. Compared with other cell types, human mesothelial cells are unusually susceptible to simian virus 40-induced malignant transformations; 50% to 60% of human mesotheliomas contain and express simian virus 40's DNA and proteins. The presence of simian virus 40 in mesothelioma has been associated with activation of specific oncogenic pathways, direct induction of telomerase activity, and down regulation of the tumor suppressor p53.

Approximately 250 to 400 cases of malignant peritoneal mesothelioma (MPM) are diagnosed annually in the United States. However, the association between asbestos exposure and MPM is weaker than that between asbestos exposure and other types of mesothelioma; only 29% to 58% of males and 2% to 23% of female patients with MPM report known asbestos exposure. Other environmental exposures associated with an elevated risk of developing MPM include thorium, talc, erionite, and mica. Simian virus 40 may also contribute to the development of MPM.

Clinical Presentation

Patients with MPM present with nonspecific signs and symptoms, including abdominal pain, swelling, anorexia, weight loss, and ascites. A characteristic paraneoplastic syndrome associated with MPM may include thrombocytosis, hypoglycemia, venous thrombosis, hepatopathy, wasting syndrome, fevers, and night sweats. In half of patients, MPM spreads in confluent sheets over the parietal and visceral peritoneum, encasing abdominal organs and creating a dominant, solid, heterogeneous, enhancing, soft-tissue peritoneal mass with little to no ascites, creating a "dry" appearance on CT studies. This presentation is commonly associated with abdominal pain. In contrast to the masses seen in pleural mesothelioma, the masses seen in this presentation of MPM are not usually calcified. In the other half of patients presenting with MPM, significant abdominal distension occurs; patients have mild to moderate volumes of ascites on CT studies and widespread peritoneal nodules without a predominant mass, a so-called "wet" presentation. In MPM, presentation type does not correlate with histologic subtype or prognosis, and a precise diagnosis based on imaging findings alone is not possible.

Diagnosis

Given its nonspecific symptoms, MPM is not easy to diagnose; the mean time between the presentation of symptoms and diagnosis is 122 days. The cytology of the ascites in "wet" MPM rarely leads to a definitive diagnosis; therefore, a diagnostic laparoscopy is often necessary because there are few or no peritoneal tumor nodules to biopsy. Because port-site recurrence is commonly observed at trocar sites, we recommend placing trocars along the linea alba to facilitate resection at the time of CRS and HIPEC. For "dry" MPM, an image-guided biopsy of the dominant mass is usually successful. Even when tissue is obtained, establishing a histologic diagnosis of MPM often requires the use of several immunohistochemical stains; no marker by itself is diagnostic. MPM is characterized by positive staining for EMA, calretinin, WT1, cytokeratin 5/6, antimesothelial cell antibody-1, and mesothelin. Cytokeratins can help to confirm invasion and distinguish mesothelioma from sarcoma and melanoma. Serum markers may also be elevated in MPM. These include mesothelin-related protein (elevated in 84% of cases), CA 125 (elevated in 58%), CA 15-3 (elevated in 50%), and CA 19-9 (elevated in 2.3%). Because of their low sensitivity

and specificity, these tumor markers are best used for surveillance rather than diagnostic purposes.

Pathology

Epithelioid is the most common histologic subtype of MPM (60% of cases), followed by sarcomatoid (20%) and biphasic (20%). Epithelioid mesothelioma can grow in four different morphologic patterns: tubular, papillary, diffuse, and deciduoid. These morphologic patterns have no influence on prognosis. Epithelioid mesothelioma, which typically is confined to the peritoneal cavity, is locally expansive without invading solid organs, and not prone to hematogenous or lymphatic metastasis, is commonly associated with a better prognosis than the other subtypes. Therefore, treating it with CRS and HIPEC with curative intent is recommended. In contrast, sarcomatoid mesothelioma, named after its sarcoma-like proliferation of spindle cells, is more commonly associated with asbestos exposure and is more likely to have calcified plaques. The prognosis for patients with this type of mesothelioma is dismal; their median overall survival duration is 5 months, regardless of treatment. Biphasic mesothelioma demonstrates both epithelioid and sarcomatoid features within single tumors. Its natural history tends to mimic that of sarcomatoid mesothelioma, that is, it often leads to locally aggressive and bulky disease that may invade solid organs. It is unclear whether the poor prognoses of biphasic and sarcomatoid mesothelioma are attributable to aggressive growth patterns, frequent chemoresistance of mixed/sarcomatoid tumors, or other biologic factors. Finally, there are two rare forms with borderline malignant potential: well-differentiated and multicystic. These unique forms of MPM typically occur in women who have not been exposed to asbestos. Unfortunately, these tumors are not well understood and can cause considerable pain and impairment in QOL. Although they are not invasive, these forms of MPM have a high tendency toward local recurrence, and malignant transformation has also been described. Therefore, complete CRS and HIPEC are advocated for patients with these tumors, as well.

Staging

There is no accepted system for staging MPM, as the eighth edition of the AJCC *Cancer Staging Manual* does not specifically address peritoneal

mesothelioma. However, eight international institutions recently proposed a tumor-node-metastasis–based staging system that resulted in significant stratification of survival by stage. The proposed staging system replaces the traditional T classification with the PCI: T1 corresponds to PCI 1 to 10, T2 corresponds to PCI 11 to 20, T3 corresponds to PCI 21 to 30, and T4 corresponds to PCI 30 to 39. Any positive lymph nodes are classified as N1 and any extra-abdominal metastases are classified as M1. Overall survival for stage I patients with T1 PCI 1 to 10 N0 M0 is significantly superior to the overall survival durations in patients in the other groups. Overall survival in patients with T2 PCI 11 to 20 and T3 PCI 21 to 30, in the absence of N1 or M1 disease, is similar, and therefore individuals meeting these criteria are categorized as stage II. Overall survival in patients with T4 PCI 30 to 39, N1, and/or M1 is also similar and is poor, and individuals in this group are therefore categorized as stage III. The 5-year overall survival rates are 87% for stage I, 53% for stage II, and 29% for stage III disease. The proposed staging system was found to be an independent predictor of survival but has not been subsequently validated. Important prognostic factors to consider in determining which MPM patients should undergo CRS and HIPEC include epithelioid histology, low disease burden (PCI <17), the likelihood of achieving complete cytoreduction, whether the patient's age is <60 years, whether the duration of environmental asbestos exposure was <20 years, and whether the patient's ECOG performance status is <2. A nomogram that includes histologic subtype, pre-CRS PCI, and preoperative serum CA 125 has been developed and demonstrated to correlate with overall survival, but it has not been subsequently validated and therefore is not largely used. Recently, Ki-67 has been demonstrated to be a powerful independent prognosticator that, along with the PCI score and histologic subtype, predicts overall survival in patients with MPM. One particular study found that patients with a Ki-67 >9 % and a PCI score >17 are unlikely to benefit from CRS and HIPEC.

Treatment

Our treatment algorithm for peritoneal mesothelioma is shown in Figure 11.5. Briefly, patients are evaluated with a history, physical examination, assessment of CA 125, and high-quality imaging (CT or MRI). Pathologic results are carefully reviewed, and the patient's case is discussed during a multidisciplinary conference. For patients with epithelioid MPM, the CT

imaging is reviewed and the likelihood of obtaining a complete cytoreduction is determined. If complete cytoreduction is likely, and if the patient has an ECOG status <2, limited comorbidities without renal insufficiency, bicavitary disease, or significant lymph node involvement then the patient is offered CRS and HIPEC with cisplatin for 60 minutes. We utilize a renal protective strategy that includes; perioperative fluid hydration, avoidance of perioperative CT imaging with contrast, avoidance of nephrotoxic medications, and the use of sodium thiosulfate at the time of HIPEC and during the subsequent 12 hours. Implementation of this strategy has greatly reduced cisplatin-related nephrotoxicity in our experience. We recommend upfront CRS and HIPEC for potentially completely resectable patients with epithelioid mesothelioma as neoadjuvant chemotherapy has not been demonstrated to be beneficial and could be harmful in patients who are immediately resectable. However, patients with epithelioid MPM who are not initially deemed likely to achieve a complete cytoreduction are treated with neoadjuvant systemic chemotherapy with cisplatin and pemetrexed and are then reevaluated for candidacy for CRS and HIPEC.

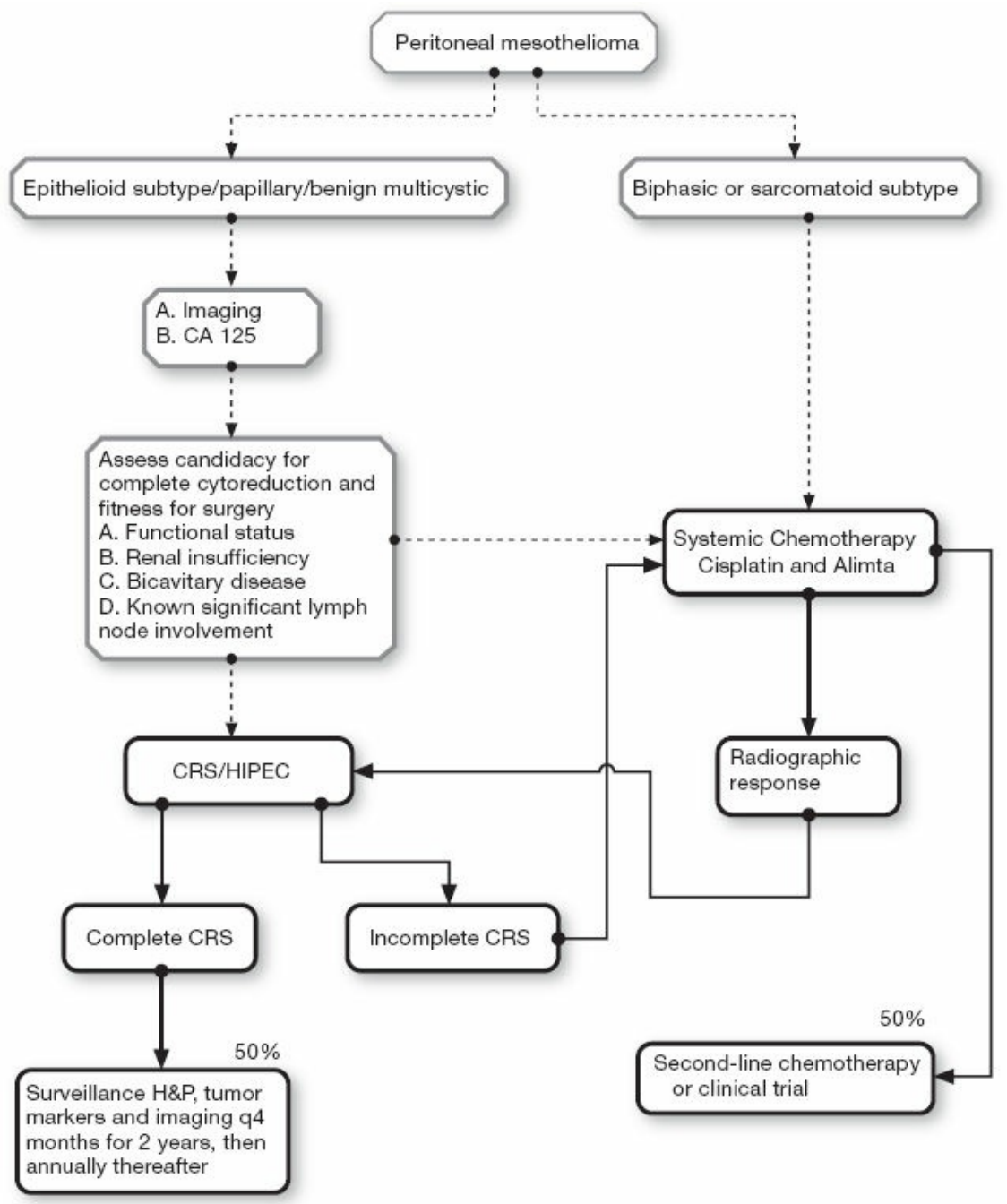

Figure 11.5 Algorithm for the multidisciplinary management of malignant peritoneal mesothelioma.

All patients with biphasic MPM are offered neoadjuvant systemic chemotherapy with cisplatin and pemetrexed to evaluate tumor biology. Patients with a good radiographic response who are deemed likely to achieve a complete CRS are then offered CRS and HIPEC with cisplatin if they have an ECOG status <2, limited comorbidities without renal insufficiency, bicavitary disease, or significant lymph node involvement. Patients with sarcomatoid MPM are not offered CRS and HIPEC and are

given palliative systemic chemotherapy. Surveillance for all surgically resected patients consists of a history, physical examination, assessment of CA 125, and CT imaging every 4 months for the first 2 years. Thereafter, they are monitored every 6 months until the 5-year mark is reached, after which annual surveillance is continued.

TABLE 11.1 Clinical Trials of Systemic Chemotherapy for Malignant Peritoneal Mesothelioma. Median Overall Survival (OS), Response Rate, and Grade III/IV Complications Are Reported

Study	Median OS	Response Rate (%)	Grade III/IV Complications
Ifosfamide/mesna	6.9	3	50%
Doxorubicin/ifosfamide	7	32	36%
Cisplatin/MMC	7.7	26	40%
Ralitrexed/cisplatin	7.7	20	30% stopped treatment due to toxicity
Cisplatin/doxorubicin	8.8	14	40%
Ironetcan	9.3	0	43%
Sorafenib	9.7	6	24%
Tremelimumab	10.7	7	14%
Cisplatin/IFN α2a	12	38	70%
Gemcitabine/cisplatin/ bevacizumab	15.6	24	42%
Gemcitabine/ pemetrexed	26.8	15	60%

Outcomes

Systemic chemotherapy is associated with low response rates (0% to 32%) and significant toxicity (24% to 60% grade III/IV toxicity) in patients with MPM (Table 11.1), but the adoption of CRS and HIPEC has resulted in improved outcomes for these individuals. Multiple single-institution series of patients with MPM treated with CRS and HIPEC have reported median overall survival durations of 30 to 92 months; this compares favorably to the results of systemic chemotherapy trials for MPM, which have reported median overall survival durations of 6 to 15 months (Table 11.2). Although a randomized, controlled trial comparing systemic chemotherapy and CRS and HIPEC has not yet been done, a recent systematic review and meta-analysis of 1,047 patients concluded that patients treated with intraperitoneal cisplatin had an improved 5-year overall survival rate.

Despite these encouraging survival results, approximately 40% to 60% of patients developed disease progression at a median of 11 to 28 months following comprehensive treatment. The majority of patients (82%) experience peritoneal-only recurrence; involvement of the pleura, liver, and/or lymph nodes is rare. Unfortunately, the small bowel is frequently involved (71% of patients) limiting the utility of repeat CRS and HIPEC (only 8% of patients with recurrent disease underwent repeat CRS and HIPEC at the National Cancer Institute of Milan). The only independent predictor of disease progression is an incomplete (>2.5 mm) cytoreduction. Recurrent disease is most commonly treated with systemic chemotherapy, however repeat CRS and HIPEC is associated with improved survival and similar morbidity to the first CRS and HIPEC in highly selected patients. Independent predictors of reduced survival following progression include a time-to-progression <9 months, poor performance status, and a need for supportive care.

TABLE 11.2 Clinical Studies of Cytoreduction and Intraperitoneal-Heated Chemotherapy for Malignant Peritoneal Mesothelioma. Median Overall Survival (OS), and 3- and 5-year Survivals Are Reported

			Survival	
Study	n =	Median OS (months)	3-year (%)	5-year (%)
Blackham (2010)	38	41	56	17
Brigand (2006)	15	36	43	29
Baratti (2010)	83	44	*	50
Feldman (2003)	49	92	59	59
Yan (2006)	100	52	55	46
Kluger (2010)	47	55	62	49
Tudor (2010)	20	30	46	*
Yan (2009)	401	53	60	47

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12 Cancer of the Colon, Rectum, and Anus

Callisia N. Clarke, Y. Nancy You, and Barry W. Feig

EPIDEMIOLOGY

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality. It is the third most commonly diagnosed cancer and the third leading cause of cancer deaths in both men and women in the United States. There are approximately 134,490 new cases of CRC diagnosed annually including 95,270 colon cancers and 39,220 rectal cancers. Efforts aimed at prevention, screening, and early detection have resulted in a significant decrease in CRC incidence of about 3% to 4% per year over the past 15 years. Despite these improvements, CRC still accounts for just over 49,000 deaths per year in the United States as well as for 8% of overall cancer deaths.

In the United States, the lifetime risk of developing CRC is about 5% with men having a 25% higher predilection when compared to their female counterparts. Age is a major risk factor in the development of sporadic CRC. Approximately 90% of all CRCs are diagnosed in patients aged 50 or greater. At the time of diagnosis, 40% of patients will have localized disease, 37% will have regional spread, and 20% have distant metastasis. The overall survival (OS) rates for CRC are highly dependent on disease stage at diagnosis, with 5-year survival for local, regional, and metastatic disease approximately 90%, 70%, and 12%, respectively.

However, recent data from the US Surveillance, Epidemiology, and End Results Reporting (SEER) database suggest that CRC incidence is increasing in patients younger than age 50 and that these young patients tend to present with more left-sided and rectal cancers when compared to the overall CRC patient population. These patients also tend to present with more advanced disease and many are symptomatic at the time of diagnosis. Current guidelines recommend endoscopic screening beginning at age 50 years for patients at average risk for CRC. There is currently no recommendation for routine CRC screening in patients under age 50 unless

there is a known underlying inherited syndrome or a family history of CRC.

RISK FACTORS

Age

Advanced age predisposes to CRC development. CRC incidence increases progressively after age 40 and rises exponentially after age 50. More than 90% of new CRC cases and 94% of CRC deaths occur in patients over age 50 years. The incidence of CRC in patients aged >60 years is 50-fold higher than patients <40 years.

Race

In the United States, CRC incidence and mortality are highest among African Americans when compared to all other ethnic/racial groups. African-American men and women have a 20% higher CRC incidence and 45% higher CRC mortality when compared to their white counterparts. CRC incidence and mortality among all other major ethnic/racial groups are lower than those seen in whites.

Although there has been a national decline in CRC rates in the last decade, this decline has been disproportionate within demographic subpopulations. The disparity is likely linked to variations in access to screening and advanced treatment modalities, as well as multifactorial reasons. For example, African Americans in general are less likely than whites to receive the most appropriate surgery, adjuvant chemotherapy, and radiation treatments after a cancer diagnosis; however in some clinical trial settings, where treatment variation is eliminated, these racial differences in survival disappear. Socioeconomic status is a major confounder, using the type of insurance as a surrogate for economic status, studies have shown that the 5-year survival for CRC is 30% higher among African-American patients who are privately insured when compared to those without health insurance.

Diet

Many dietary factors have been studied regarding their effect on CRC. Consumption of red meat, processed meat, and animal fat, as well as the presence of high fecal levels of cholesterol, correlate with an increased risk

of CRC. In 2015, the World Health Organization declared red meat and processed meat as probable carcinogens. In addition, some studies suggest that people who eat a diet low in natural fiber and low in fruits and vegetables have a higher risk of CRC. Differences in dietary fiber intake have been hypothesized to contribute significantly to geographic differences in CRC incidence between Africa and Westernized countries. Additionally, an increased risk of CRC development has also been linked to moderate alcohol consumption (30 g or approximately 2 drinks/day). Conversely, folate supplements have been shown to be protective against CRC. Calcium supplements have been shown to decrease the formation of new adenomas in patients with a history of adenomas as well as reduce the risk of CRC. Vitamins with antioxidant properties including beta-carotene, vitamins A, C, E, and selenium have been studied, and at present there are no prospective data that demonstrate a protective effect when these vitamins are derived from food sources, but a daily multivitamin supplement showed a relative risk reduction for CRC with its use.

Physical Activity and Obesity

Physical inactivity and obesity are two modifiable lifestyle-related risk factors linked to the development of CRC and are believed to contribute to one-third of CRCs. Regular physical activity has been shown in several studies to decrease the risk of CRC with the strongest evidence noted in colon cancer when compared to rectal cancer. The biologic mechanisms are still being elucidated however the metabolic effect of activity on insulin resistance and gut motility have been implicated. Obesity, specifically excess central adiposity, has been shown to correlate with increased circulating insulin and decreased insulin sensitivity, both of which are believed to increase cancer risk.

Cigarette Smoking

Cigarette smoking contributes to the development of adenomatous polyps, particularly more aggressive adenoma precursor lesions for CRC. Some studies have shown that long-term smoking increases the risk of developing CRC, particularly rectal cancer, and also demonstrate an earlier average age of onset of CRC in cigarette smokers.

Medications

Several medications have demonstrated protective effects for CRC. Hormone replacement therapy has been shown to significantly decrease mortality from CRC in women. Aspirin and other nonsteroidal anti-inflammatory drugs have also demonstrated protective effects. Recent studies with sulindac and the selective cyclooxygenase-2 inhibitor celecoxib demonstrated the ability of these agents to cause regression of colon polyps in patients with FAP. However, the cyclooxygenase-2 inhibitors have been associated with an increased risk for cardiovascular complications; therefore, their role in chemoprevention remains unclear.

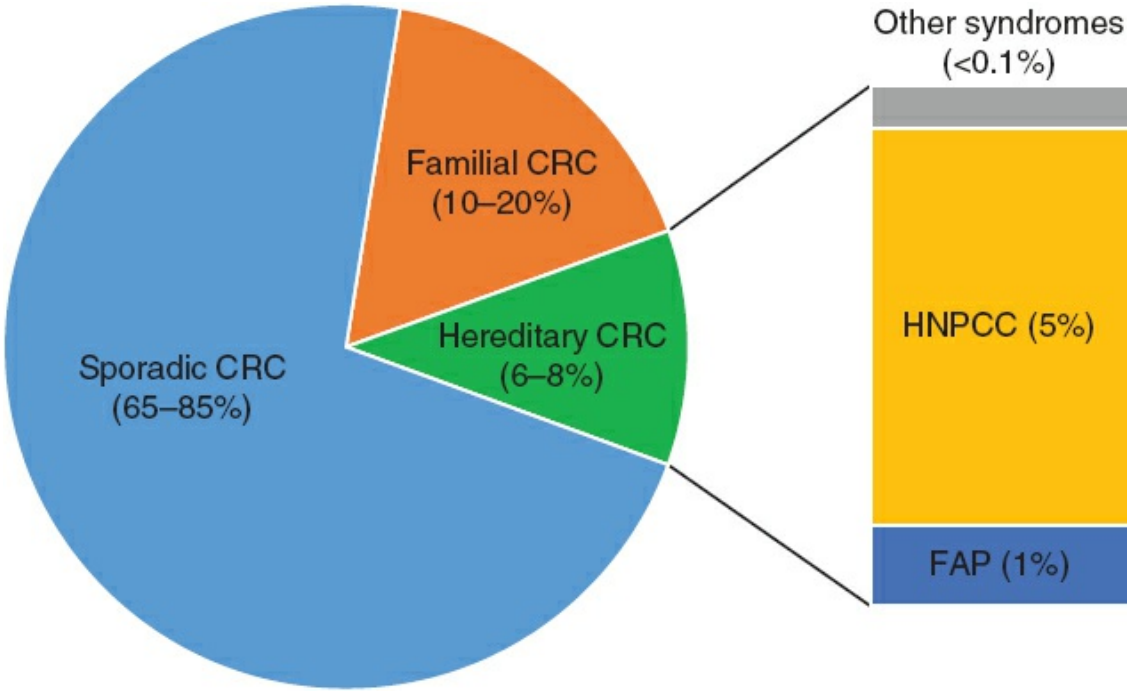

Figure 12.1 Pie chart showing proportion of CRC cases believed to be sporadic, familial or due to hereditary cancer syndromes. HNPCC, hereditary nonpolyposis colon cancer; FAP, familial adenomatous polyposis.

COLORECTAL TUMORIGENESIS

The majority of CRCs arise as sporadic cancers in patients without a significant family history of CRC (Fig. 12.1). An additional 10% to 20% are associated with a familial predisposition with no identifiable hereditary mutation. Only a small fraction of colorectal cases can be directly attributed to known genetic syndromes such that true hereditary CRC accounts for less than 10% of patients diagnosed with the disease. Hereditary CRC syndromes arise from inheritable germline mutations and

are typically associated with well-characterized clinical presentations. Hereditary nonpolyposis CRC (HNPCC) and familial adenomatous polyposis (FAP) are the most common syndromes encountered in practice. Other rarer syndromes that predispose to CRC and are outlined in Table 12.1 and are briefly discussed below.

Hereditary CRC Syndromes

Hereditary Nonpolyposis CRC

HNPCC or Lynch syndrome is the most commonly inherited rectal cancer syndrome. It had been reported to account for 2% to 5% of all CRCs (Fig. 12.1). This autosomal dominant syndrome results from germline mutations in DNA mismatch match repair (MMR) genes leading to accumulation of mutations predisposing to the development of colorectal, endometrial, and other cancers. A molecular signature of MMR mutations is the finding of microsatellite instability in the tumor. Mutations in *MLH1* and *MSH2* account for nearly 90% of all Lynch syndrome patients, with mutations in *MSH6*, *PMS2* and *EPCAM* accounting for the remainder of cases. Patients typically inherit one germline MMR gene mutation and subsequently acquire an inactivating mutation in the remaining allele. For this reason, penetrance varies widely within families ranging from 30% to 70%. The risk of developing a CRC by the fourth and fifth decades of life approaches 80%. At the time of diagnosis, approximately 20% of patients will have synchronous tumors so careful evaluation of the entire colon and rectum prior to surgical intervention must be performed in patients with HNPCC presenting with a cancer. When planning surgical resection, consideration should be given to extending the resection to beyond a segmental colectomy with the intent of preventing future CRCs. Indeed, about 20% to 60% of patients with will develop a metachronous CRC after initial resection if a subtotal colectomy is not performed. In patients with Lynch syndrome, the time it takes for an adenoma to progress to malignancy is shorter then the time frame seen in patients with sporadic colon cancer. Therefore, endoscopic clearance of all adenomas is extremely important in patients with Lynch syndrome. Another clue to possibility of Lynch syndrome being the underlying driving factor of tumorigenesis is the development of adenomatous polyps at an early age. HNPCC also increases the risk of developing other cancers including endometrial, ovarian, gastric, and hepatobiliary malignancies.

TABLE 12.1

Genetic Syndromes with an Inherited Predisposition to Development of CRCs

Syndrome	Mutations	Life Time CRC Risk	Age at Dx	Phenotype
Nonpolyposis Syndromes				
Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome	MLH1 (30–40%) MSH2 (50%) MSH6 (7–10%) PMS2 (5%) EPCAM (1–3%)	50–80%	40–60 years	Synchronous tumors Microsatellite unstable tumors (MSI-H) Other associated cancers: Endometrial, ovarian, stomach
Autosomal dominant inheritance				
Adenomatous Polyposis Syndromes				
Familialadenomatous polyposis (FAP)	APC	≈100%	30–40 years	100–1,000s adenomatous polyps, duodenal and gastric polyps (fundus) Congenital hypertrophy of retinal pigment epithelium
Autosomal dominant inheritance				
Gardner	APC	≈100%	30–40 years	Same as FAP—simply a phenotypic variant Additionally associated with desmoid tumors (15%), osteomas of the skull and thyroid cancer
Autosomal dominant inheritance				
Turcot's	APC (60–70%)	50–100%	20–40 years	Same as FAP—colon polyps, CRC and CNS tumors primarily medulloblastoma
Autosomal dominant inheritance	MLH1, PMS (30%)			Lynch type—no polyps, CRC and CNS tumors primarily glioblastoma multiforme
Attenuated familial adenomatous polyposis coli	APC	Unknown	50 years	<100 polyps Right-sided tumors and polyps with rectal sparing
Autosomal dominant inheritance				
MYH-associated polyposis	MYH	80%	50 years	10–100s adenomatous polyps Somatic KRAS mutation (G12C) Microsatellite stable tumors (MSS)
Autosomal recessive inheritance				
Hamartomatous Polyposis Syndromes				
Juvenilepolyposis	SMAD4/DPC4 BMPR1a	60–70%	60 years	Hamartoma of colon and stomach, GI bleed, children <10 years Associated with facial abnormalities including cleft lip or palate and macrocephaly
Autosomal dominant inheritance				
Peutz–Jeghers	LKB1 STK11	85%	50 years	Hamartomatous GI polyps, hyperpigmented macules on the lips and oral mucosa, breast caner
Autosomal dominant inheritance				
Cowden	PTEN	16%	50–60 years	Hamartomas of skin, mucous membranes, thyroid, breast
Autosomal dominant inheritance				

When compared to sporadic CRC, patients with HNPCC will present with more right-sided cancers (60% to 70% occur proximal to the splenic flexure), at a younger age (≈45 years of age), and have an increased rate of metachronous and synchronous tumors (20%). Impaired DNA repair results in microsatellite repeat replication errors that to go unchecked, thereby inactivating tumor suppressor genes and leading to genetic instability. These resulting cancers are characterized by a high level of microsatellite instability (MSI-H). In general, they present at a lower tumor stage and afford a better overall prognosis when compared to microsatellite stable tumors.

A major challenge in the management of patients with HNPCC is the identification of those individuals who should be tested. A detailed family history should be obtained in all patients with CRC and may identify high-risk conditions where the patients would benefit from genetic counseling. Potentially affected individuals may also be identified by screening using Amsterdam criteria or Bethesda guidelines (Table 12.2). Although lacking

in specificity, the use of these criteria and guidelines is associated with 60% to 94% sensitivity for identifying individuals with HNPCC. At the MD Anderson Cancer Center (MDACC), we advocate for universal screening, testing for MMR gene protein expression in all colorectal tumors. If loss of protein expression is noted, genetic counseling and confirmatory germline testing should be performed. The treatment of HNPCC begins with early surveillance. Screening colonoscopy in affected individuals should begin by 20 to 25 years of age and should be repeated every 1 to 2 years. Surgical treatment of patients with HNPCC and confirmed colon cancer should favor subtotal colectomy with ileorectal anastomosis (IRA). Annual surveillance of the remnant rectum is indicated thereafter. Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be discussed as an option in women after the completion of childbearing.

Familial Adenomatous Polyposis

FAP is the second most commonly inherited CRC syndrome accounting for about 1% of all CRCs. It is an autosomal dominant genetic disorder that results from a germline mutations in *APC*. Classic FAP manifests with hundreds to thousands of colorectal adenomas beginning in adolescence that develop into CRCs almost universally by the fourth decade of life. Most patients will present with a strong history of early colon cancers in first- and second-degree relatives, though about 25% of patients will present as the proband due to “de novo” APC gene mutations. The lifetime incidence of CRC in patients with FAP approaches 100%.

Prophylactic surgery is essential, especially in patients with classic FAP, to decrease mortality related to CRC. Preventative surgery should be considered when the polyp burden exceeds the ability for endoscopic clearance or surveillance, when there is evidence of dysplasia, and by patient preference, but typically by the fourth decade. Prophylactic surgery should consider either total proctocolectomy with ileoanal pouch anastomosis or total abdominal colectomy with ileorectal anastomosis and must balance the polyp and disease burden in the rectum, the extent of surgery, with long-term quality of life. Prophylactic colorectal resection must be followed up by frequent surveillance of the remaining GI tract to identify other precancerous polyps. Although as many as 90% of patients can develop polyps in the upper GI tract, particularly the duodenum, only about 5% of duodenal polyps progress to invasive carcinomas. Duodenal

adenocarcinoma is the most common cause of death in FAP patients who have had prophylactic colorectal surgery.

Variants of classic FAP, arising also from *APC* gene mutations, have been described, and similarly predispose to development of CRC (Table 12.1). There are genotype–phenotype correlations between the severity of disease and the nature of the APC mutations. Attenuated adenomatous polyposis coli (aFAP) is often described as a less aggressive variant of FAP. These patients develop fewer polyps, typically confined to the proximal colon and rarely affect the rectum. CRCs can manifest later in the fifth decade of life.

TABLE 12.2 Amsterdam Criteria and Bethesda Guidelines

Amsterdam I

At least three relatives must have histologically verified colorectal cancer

1. One must be a first-degree relative of the other two
2. At least two successive generations must be affected
3. At least one of the relatives must have received the diagnosis before age 50

Amsterdam II

Similar to Amsterdam I, but may include any combination of cancers associated with HNPCC (e.g., colorectal, endometrial, gastric, ovarian, ureter or renal pelvis, brain, small bowel, hepatobiliary tract, sebaceous gland adenomas, keratoacanthomas)

Bethesda Guidelines

1. Amsterdam criteria are met
2. Two colorectal or HNPCC-related cancers, including synchronous and metachronous presentation
3. Colorectal cancer and a first-degree relative with colorectal and/or an HNPCC-related cancer and/or a colonic adenoma; one of the cancers must be diagnosed before age 45 and the adenoma diagnosed before age 40
4. Colorectal or endometrial cancer diagnosed before age 45
5. Right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology, diagnosed before age 45
6. Signet ring cell–type colorectal cancer diagnosed before age 45 (>50% signet ring cells)
7. Colorectal adenomas diagnosed before age 40

Revised Bethesda Guidelines

1. Early-onset colorectal cancer (before age 50)
2. Synchronous, metachronous, or other HNPCC-associated tumors, regardless of age
3. Colorectal cancer with high microsatellite instability diagnosed before age 60
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed before age 50
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Other Inherited CRC Syndromes

Table 12.1 summarizes other hereditary syndromes that predispose to the development of CRC. MYH-associated polyposis is an autosomal recessive disorder that results from biallelic germline mutations in *MYH*, a base excision repair gene. For this reason, patients typically will not have a generational family history of cancers but most will develop CRC before age 60 years. Other syndromes result in hamartomas of the colon and rectum with varying lifetime risk of development of CRC. *SMAD4*, *PTEN* and *STK11* are several of the genes implicated in the development of these tumors and also play a role in the development of sporadic CRC.

Sporadic CRC

Advances in molecular biology have increased our knowledge of the genetic and epigenetic events that drive CRC tumorigenesis. The Cancer Genome Atlas Network (TCGA) in their recent comprehensive molecular analysis of CRC demonstrated that colon and rectal cancers are molecularly indistinguishable and identified two distinct subtypes; nonhypermutated and hypermutated with unique genetic signatures. These and other investigations have led to the identification of multiple pathways that lead to the development of CRC (Fig. 12.2). The classic adenoma-to-carcinoma pathway was initially described by Vogelstein and colleagues. Approximately 70% of sporadic CRC arise via this adenoma-to-carcinoma progression, driven by loss of APC and/or p53 tumor suppressor genes with accumulation of chromosomal instability over time. A second pathway involves the loss of DNA mismatch repair and is exemplified by the germline mutations seen in Lynch syndrome or by acquired MLH1 methylation. BRAF appears to act via a third pathway; the serrated/methylator pathway tumors are characterized by the methylation of CpG islands that cause the silencing of critical tumor suppressor genes resulting in CpG island methylator phenotype (CIMP) tumors. The CRC Subtyping Consortium (CRCSC) has worked to further characterize the genetic and epigenetic features of CRC by integrating tumor mutation status, DNA copy number variations, gene methylation, microRNA, and protein expression. This effort has better elucidated CRC tumor heterogeneity and may have direct implications on patient prognosis and response to therapies. They describe four distinct consensus molecular subtypes (CMS) with unique molecular characteristics, tumor phenotype and prognosis (Table 12.3). CMS1 CRCs are predominantly MSI- high tumors and tend to be hypermutated, methylated, and/or enriched for *BRAF* mutations. CMS2 and CMS4 are driven by chromosomal instability typically resulting in microsatellite stable tumors arising from high copy number alterations. CMS4 tumors display proangiogenic properties driven by multiple pathways including vascular endothelial growth factor (VEGF) signaling. For this reason, these tumors are associated with a poor prognosis manifest as early relapse and distant failure. CMS3 tumors are driven by metabolic reprogramming, exhibiting fewer copy number alterations and enriching for mutations known to affect metabolic adaptation such as *KRAS and PIK3CA* mutations.

While the efforts of the TCGA, CRCSC, and others have significantly

improved our understanding CRC carcinogenesis, our understanding of the mutational landscape of CRC continues to evolve. There remains a need to identify and validate novel translational paradigms to accurately subtype CRC in order to allow for a truly personalized approach to treatment.

CRC SCREENING

Screening Guidelines and Methods

The overall incidence of CRC is decreasing in the United States; this has been largely attributed to population-based screening for CRC. As previously discussed, the vast majority of CRCs arise via the classic adenoma-to-carcinoma pathway so that the identification and timely removal of premalignant lesions can prevent progression to carcinoma. Current guidelines for CRC screening and surveillance as recommended by the US Multi-Society Task Force are outlined in Table 12.4. Screening should be initiated at age 50 for patients with average CRC risk. African Americans are more likely to be develop CRC than other populations and tend to present at a younger age. For this reason, some experts advocate initiating screening at age 45 years in this population. The goals of screening are detection of early cancers and prevention of cancer by finding and removing adenomas. Factors predisposing to developing CRC included personal history of polyps, personal history of CRC, or family history of CRC or polyps. Patients with known or suspected hereditary CRC syndromes, and patients with longstanding inflammatory bowel disease are considered high risk for CRC. These patients warrant special considerations which are summarized in Table 12.4.

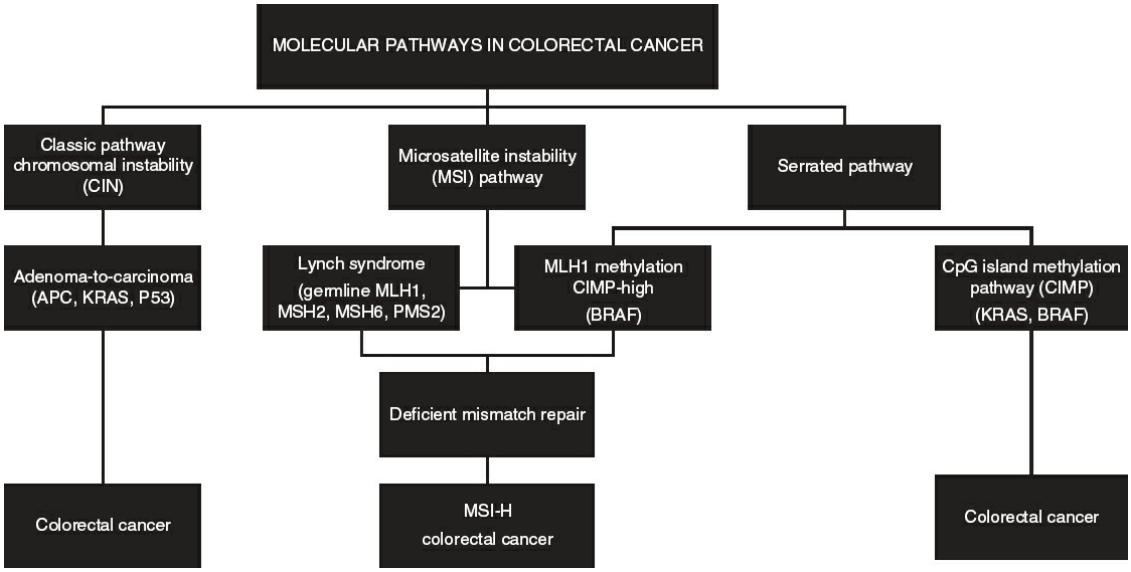

Figure 12.2 CRCs develop via three distinct molecular pathways. The classic or chromosomal instability (CIN) pathway accounts for 30% to 70% of CRCs resulting from adenoma progressing to carcinoma. Germline mismatch repair mutations lead to Lynch syndrome, which accounts for approximately one-quarter of all MSI CRCs. The Serrated/Methylated pathway is driven by hypermethylation.

TABLE **12.3** Consensus Molecular Subtype (CMS) Classification of CRC

Consortium Subtype	Molecular Features	Clinical Characteristic	Incidence (%)
CMS1 MSI Immune	Hypermutated MSI—high CIMP—high BRAF mutated Immune activation/ expression	Right-sided tumors Older age at diagnosis Females Intermediate survival Worse survival after relapse	14
CMS2 Canonical	High CIN MSS WNT/MYC pathway activation TP53 mutated EGFR amplification/ overexpression	Left-sided tumors Better survival	37
CMS3 Metabolic	CIN-low Mixed MSI and MSS tumors Metabolic derangement KRAS mutated PIK3CA mutated IGFBP2 overexpression	Intermediate survival	13
CMS4 Mesenchymal	CIN-high MSS TGF-beta activation NOTCH3/VEGFR2 overexpression	Stromal infiltration Younger age at diagnosis Worse relapse-free and overall survival	23

Multiple methods of CRC screening are currently employed in average-risk patients with demonstrated efficacy and sensitivity. Endoscopic screening tools are most frequently utilized as they offer diagnostic and therapeutic options. Flexible sigmoidoscopy (FSIG) allows for endoscopic examination of the distal colon and rectum. Case-control studies have demonstrated a 60% to 80% reduction in CRC mortality with routine FSIG screening over nonscreened counterparts. This is because most sporadic CRCs arise the left colon or rectum. However, FSIG is only effective for the area inspected and should be performed with insertion of the endoscopy to at least 40 cm or to the splenic flexure to be considered adequate. FSIG as a screening tool has found favor because it can be easily performed. The procedure is often done in the office without sedation and patients often undergo simple bowel preparation in the form of enemas. As a screening test, flexible sigmoidoscopy, when normal, should be repeated every 5 years. Because of its limited evaluation of the colon, FSIG is often

used in conjunction with radiographic evaluation of the more proximal colon or annual fecal occult blood testing. If polyps are found on FSIG, a full colonoscopy is warranted.

Colonoscopy is one of the most frequently performed procedures in the United States. This involves inspection of the entire rectum and colon to the ileocecal valve. Given that up to 40% of colon cancers arise proximal to the splenic flexure, colonoscopy offers added sensitivity of CRC detection over FSIG. Most studies using screening colonoscopy in average-risk patients report an average of 30% of neoplastic lesions detected, the majority of which are amenable to endoscopic removal. Limitations of colonoscopy include the need for prolonged bowel preparation and dietary restrictions, need for sedation and monitoring and wide variation in operator-skill. Cost is also an important consideration, however, studies have shown screening colonoscopy to be cost-effective if a 10-year interval is used and if the colon is appropriately cleared of polyps. Despite these limitations, colonoscopy remains the gold-standard for examination of the colon and rectum. All positive findings found with other screening modalities require a colonoscopy to definitively assess and/or clear the colon.

TABLE **12.4** US Multi-Society Task Force on CRC Guidelines for Colonoscopy Screening and Surveillance

Patients with Average Risk

Screening beginning at age 50 years (consider screening at age 45 years for African Americans) with one of the following:

- Colonoscopy every 5–10 years
- Flexible sigmoidoscopy (FSIG) every 5 years
- Double contrast barium enema (DCBE) every 5 years
- Computed tomography colonography (CTC) every 5 years
- Fecal occult blood test (FOBT) annually
- Fecal immunochemical testing (FIT) annually

Patients at Increased Risk due to Personal History of Polyps

Risk Category	Recommendation
Small rectal hyperplastic polyps	Same as average risk
1–2 small (<1 cm) tubular adenomas with low grade dysplasia	Colonoscopy 5–10 years after polypectomy
3–10 small adenomas	Colonoscopy 3 years after complete polypectomy
Any adenoma >1 cm	
Any adenoma with high-grade dysplasia	
Any adenoma with villous features	
>10 adenoma on a single examination	Colonoscopy <3 years after polypectomy
Sessile adenomas removed in pieces	Colonoscopy 2–6 months to verify complete excision

Patients at Increase Risk due to Personal History of Sporadic CRC	
Risk Category	**Recommendation**
At time of CRC diagnosis	• Colonoscopy aimed at evaluating the entire colon preoperatively to rule out synchronous cancer and remove premalignant polyps • If unable to traverse the tumor due to obstruction Colonoscopy within a 3–6 month interval after surgery
Surveillance after curative CRC resection	• Colonoscopy 1 year after surgery or 1 year after clearing perioperative colonoscopy • Next colonoscopy after a 3-year interval (4 years after surgery) • Subsequent colonoscopies every 5 years * If polyps are found the recommended interval for polyp surveillance above should be performed
Patients at Increased Risk due to Family History of CRC	
Risk Category	**Recommendation**
CRC or adenomatous polyp in first-degree relative <60 years CRC or adenomatous polyp in 2 or more first-degree relatives any age	Screening Colonoscopy beginning at age 40 years or 10 years prior to age of youngest affected immediate family member and every 5 years there after

CRC or adenomatous polyp in first-degree relative ≥60 years CRC or adenomatous polyp in 2 or more second-degree relatives any age	Screening colonoscopy beginning at age 40 years and every 10 years there after

Patients at High Risk

Risk Category	Recommendation
Familial adenomatous polyposis (FAP) confirmed or suspected	• Screening beginning at ages 10–12 years with annual FSIG • Genetic testing and counseling • Early prophylactic colectomy
Lynch syndrome (HNPCC) confirmed or suspected Known family history of HNPCC	• Screening Colonoscopy beginning at ages 20–25 years and every 1–2 years there after • Genetic testing and counseling to patient and all first-degree relative s if HNPCC confirmed
Inflammatory bowel disease (IBD) *Crohn's colitis and Ulcerative colitis*	• Consider referral to tertiary center with IBD expertise • Screen prior to 8 years after onset of pancolitis or prior to 12–15 years after onset of left-sided colitis with colonoscopy and biopsy to assess for dysplasia

Blood in the stool is a nonspecific finding but can point to large adenomas or occult tumors. Fecal occult blood tests (FOBT) can be guaiac-based (gFOBT) or immunohistochemical-based (FIT). Guaiac-based tests rely on pseudoperioxidase-mediated oxidation which is catalyzed in the presence of heme or hemoglobin. FIT utilizes antibodies to detect human globulin. Prospective randomized trials have shown that fecal occult blood screening followed by colonoscopy detects cancers at an earlier stage when compared to patients that aren't screened. The Minnesota Colon Cancer Control Study demonstrated a significantly improved cancer-related survival, and a meta-analysis of FOBT randomized trials indicates that Hemoccult testing is associated with a 15% to 43% reduction in the mortality rate from colorectal carcinoma. However, the sensitivity of FOBTs is highly variable. For this reason, two to three samples are often needed to complete the test with acceptable sensitivity. If FOBT is positive, total colonoscopy should be performed.

Double-contrast barium enema (DCBE) is used less frequently than colonoscopy for screening and can detect colorectal carcinoma and polyps greater than 1 cm with accuracy equal to that of colonoscopy. It has been used in patients who refuse or cannot have a full colonoscopy to the

cecum, as an adjunct to flexible sigmoidoscopy, to evaluate the remainder of the colon and for difficult-to-visualize turns in the colon. The difficulty with this method is that lesions detected by DCBE require further evaluation and intervention, decreasing the cost-effectiveness of the method. Current American Cancer Society screening recommendations are for DCBE every 5 years with subsequent colonoscopy if test results are positive.

Computed tomography (CT) colonography (virtual colonoscopy) has emerged as a technique for the diagnosis of colonic polyps in the screening population, that uses three-dimensional reconstruction of the air-distended colon. At the National Naval Medical Center, in 1,223 average-risk adults who subsequently underwent conventional (optical) colonoscopy, virtual colonoscopy was as good or better at detecting relevant lesions. A more recent multi-institutional study looking at 2,600 asymptomatic patients 50 years of age or older found that CT colonography identified 90% of patients with adenomas or cancers measuring 10 mm or more in diameter and further strengthened published data on the role of CT colonography in screening patients with an average risk of CRC. However, some of the major limitations included the need for full bowel preparation and follow-up colonoscopy for tissue diagnosis of radiographic abnormalities. Because virtual colonoscopy is considerably time and labor intensive from the standpoint of the radiologist, active investigations into methods of automating the evaluation process are ongoing. Current American Cancer Society screening recommendations are for virtual colonoscopy every 5 years with subsequent colonoscopy if a lesion is found.

Carcinoembryonic antigen (CEA) is a glycoprotein found in the cell membranes of many tissues, including CRC. Some of the antigen enters the circulation and is detected by radioimmunoassay of serum; CEA is also detectable in various other body fluids, urine, and feces. Elevated serum CEA is not specifically associated with CRC; abnormally high levels are also found in sera of patients with malignancies of the pancreas, breast, ovary, prostate gland, head and neck, bladder, and kidney. CEA levels are high in approximately 30% to 80% of patients with cancer of the colon, but less than half of patients with localized disease are CEA positive. Therefore, CEA has no role in screening for primary lesions. False-positive results occur in benign disease (lung, liver, and bowel). The CEA level is also increased in smokers. Overall, 60% of tumors will be missed by CEA screening alone.

Indications for Endoscopic Intervention on Screening

Polyps

Polyps represent the most frequent indication for endoscopic intervention during colonoscopy. As previously mentioned, CRCs often arise from polyps, however polyps differ and carry varying risks of malignant progression. Colorectal polyps are classified histologically as either neoplastic (which may be benign or malignant), adenomatous polyps (including serrated adenomatous) or nonneoplastic polyps (including hyperplastic, mucosal, inflammatory, and hamartomatous). Adenomatous polyps are found in approximately 33% of the general population by age 50 and in approximately 50% of the general population by age 70. Most lesions are less than 1 cm in size, with 60% of people having a single adenoma and 40% having multiple lesions. Sixty percent of lesions will be located distal to the splenic flexure. Polyps can progress to CRC via the classic or serrated molecular pathways previously discussed.

The National Polyp Study showed that colonoscopic removal of adenomatous polyps significantly reduced the risk of developing CRC. Polyps coexist with CRC in 60% of patients and are associated with an increased incidence of synchronous and metachronous colonic neoplasms. Patients with a primary cancer and a solitary associated polyp have a lower incidence of synchronous and metachronous lesions when compared to patients with multiple polyps. The natural history of polyps supports an aggressive approach to their timely removal: invasive cancer will develop in 24% of patients with untreated polyps at the site of that polyp within 20 years.

The risk of associated malignancy varies with polyp histology and size. There are three main histologic variants of adenomatous polyps (Table 12.5). Tubular adenomas are found with equal distribution throughout the colon, and carry the lowest risk of associated malignancy. Villous adenomas have a predilection for the rectum. They are much less common but carry a 35% to 40% risk of harboring an underlying malignancy. Polyps may be pedunculated (usually tubular or tubulovillous), sessile (usually tubulovillous or villous), or nonpolypoid (flat or depressed). Nonpolypoid neoplasms are more difficult to detect because of subtle similarities to normal mucosa. Depressed nonpolypoid lesions have been shown to carry a high risk of cancer at the time of diagnosis. Polyp size and the degree of dysplasia also correlate with malignant potential. Small adenomas (<1 cm) are associated with malignancy in only 1.3% of cases

while adenomas >2 cm harbor malignancy 46% of times. Similarly, higher degree of dysplasia is associated with increasing risk of malignancy; adenomatous polyps with mild, moderate, and severe dysplasia are found to have malignant cells on complete excision of the polyp in 5.7%, 18%, and 34.5% of the time, respectively.

TABLE 12.5 Neoplastic Polyps and Risk of Malignancy

Histologic Subtype	Incidence (%)	Risk of Malignancy (%)
Tubular adenoma	75–85	<5
Tubulovillous adenoma	8–15	20–25
Villous adenoma	5–10	35–40

High-grade dysplasia characterizes severely dysplastic adenomas where malignant transformation has not invaded through the muscularis mucosa and therefore this finding not carry a risk of deeper invasion or nodal dissemination. Approximately 5% to 7% of adenomatous polyps contain high-grade dysplasia and 3% to 5% harbor invasive carcinoma at the time of diagnosis. Increasing dysplasia and malignant potential correlate with increasing size, villous component, and patient age. If a polyp containing high-grade dysplasia is completely excised endoscopically, the patient may be considered cured.

Overall, 8.5% to 25% of polyps harboring invasive carcinoma will metastasize to regional lymph nodes. Unfavorable pathologic features of the malignancy increase the probability that regional lymph nodes will be involved with tumor and include (a) poor differentiation, (b) vascular and/or lymphatic invasion, (c) invasion below the submucosa, and (d) positive resection margin as defined by the presence of tumor within 1 to 2 mm from the transected margin and/or the presence of tumor cells within the diathermy of the transected margin. Approximately 4% to 8% of malignant polyps are poorly differentiated. Poorly differentiated lesions (grade 3) are associated with a higher incidence of lymphovascular involvement and recurrent disease when compared with well- and moderately differentiated lesions (grades 1 and 2, respectively). The presence of one or more of these adverse features should prompt evaluation for surgical resection. Depth of invasion is an important

prognostic factor for mesenteric lymph node involvement with invasive cancer arising in a polyp. In 1985, Haggitt et al. classified the level of invasion from the head of the polyp to the submucosa of the underlying colonic wall (Table 12.6). In a multivariate analysis, only invasion into the submucosa of the underlying bowel wall (level 4) was a significant prognostic factor. This is in keeping with previous pathologic studies that have shown that the lymphatic channels do not penetrate above the muscularis mucosa. Although these findings have been confirmed by other studies, there are frequently multiple adverse prognostic factors seen in patients with higher levels of invasion (i.e., levels 3 and 4), which makes it difficult to assign depth as the most important factor. A negative resection margin has consistently been shown to be associated with a decreased risk for adverse outcome (recurrence, residual carcinoma, lymph node metastases, and decreased survival). Twenty-seven percent of patients with positive or indeterminate tumor margins will have adverse outcomes, compared with 18% with negative margins and poor prognostic features and 0.8% with negative margins and no other poor prognostic features. Therefore, multiple risk factors should be assessed together.

TABLE 12.6 Haggitt Classification for Colorectal Carcinomas Arising in Adenomas

Classification	Depth of Invasion
0	Carcinoma confined to the mucosa
1	Head of polyp
2	Neck of polyp
3	Stalk of polyp
4	Submucosa of the underlying colonic wall

Colonoscopic polypectomy is safe and effective for excision of nearly all pedunculated polyps. For polyps not amenable to polypectomy, endoscopic mucosal resection (EMR) may be utilized and is particularly advantageous in the removal of small (not >1 cm), flat or depressed lesions. EMR results in the en bloc removal of the lesion and the deep submucosal layer, providing additional pathologic information. Furthermore, EMR alone may be sufficient treatment for early cancers without aggressive features.

Surgical resection is recommended for large sessile villous lesions.

Fungating, ulcerated, or distorted lesions destroying the surrounding bowel wall indicate the presence of invasive cancer and are contraindications to polypectomy. Surgical resection is also indicated for patients with residual invasive carcinoma and for those at high risk for lymph node metastases despite complete endoscopic polypectomy. Marking of the polyp or polypectomy site, usually in the form of tattooing, should be performed at the time of colonoscopy or within 2 weeks to improve accuracy of capturing the target lesion at the time of surgical resection.

The high-risk pathologic features previously described (margin ≤2 mm, poor differentiation, Haggitt level 4, and vascular and/or lymphatic invasion) and the associated increased risk of lymph node metastasis should be weighed against the risk of surgical resection. In a review of 17 studies to evaluate the frequency of lymph node metastases or residual carcinoma in low-risk patients with pedunculated polyps, only a 1% incidence was found. In sessile polyps with low-risk features, the incidence was increased to 4.1%. Because the incidence of nodal metastases is higher in sessile polyps with invasive cancer, those patients at low operative risk may be considered for resection even if no high-risk pathologic features are observed. Stalk invasion in pedunculated polyps is not considered an adverse histologic feature, and treatment of polyps with stalk invasion is the same as that of polyps without stalk invasion (based on risk stratification). Large villous adenomas of the rectum may be amenable to transanal local excision. This provides a complete diagnostic evaluation for malignancy, and if excised with negative margins (with other favorable prognostic features), it may be the only therapeutic procedure needed.

Inflammatory Bowel Disease

Chronic ulcerative colitis carries a risk for CRC that is 30 times greater than that of the general population. Similarly, longstanding Crohn's colitis is associated with significantly higher CRC risk. The cancer risk in inflammatory bowel disease increases significantly 8 years after the onset of pancolitis and 12 to 15 years after left-sided colitis. This risk continues to increase by 0.5% to 1% per year after 10 years and is 18% to 35% at 30 years. The severity, extent, and duration of inflammation, as well as family history of CRC and history of primary sclerosing cholangitis, are risk factors for the development of cancer. In contrast to sporadic CRCs, these cancers are more often multiple, broadly infiltrating, and poorly

differentiated. They can be extremely difficult to identify due to chronic inflammation and scarring, as well as the fact that many of them arise from dysplasia-associated lesions or masses (DALMs) which are often flat lesions easily missed during endoscopy. Surveillance colonoscopy is recommended every 1 to 2 years with random 4-quadrant biopsies every 10 cm throughout the affected area. A minimum of 33 biopsies is recommended for patients with extensive disease. In patients with ulcerative colitis, consideration should be given to taking biopsies every 5 cm in the distal sigmoid and rectum where their cancer risk is highest. Colectomy or proctocolectomy is recommended for patients when there is evidence of high-grade dysplasia and should be considered even for those with evidence of low-grade dysplasia.

DIAGNOSING CRC

Clinical Presentation

Patients with CRC can be asymptomatic (cancers found on surveillance colonoscopy) or present with symptoms such as rectal bleeding, unexplained anemia, fatigue, shortness of breath, abdominal pain, change in bowel habits, anorexia, weight loss, nausea, and/or vomiting. Pelvic pain or tenesmus may point to an advanced rectal cancer with involvement of the pelvic floor muscles or nerves. Metastatic disease may present as abdominal pain, fevers, hepatomegaly, ascites, effusions, and supraclavicular adenopathy. Central nervous system and bone metastases are seen in less than 10% of autopsy cases and are very rare in the absence of advanced liver or lung disease. The routine use of CT for *diagnosis* of CRC is discouraged because cross-sectional imaging can easily miss mural disease in the hollow viscus. Endoscopy with biopsy is recommended for histologic diagnosis. Subsequent cross-sectional imaging should be used to for clinical staging through evaluation of the abdomen and pelvis and for assessing for evidence of CRC complications such as obstruction or perforation which may warrant urgent or emergent intervention. The incidence of complete obstruction at the time of presentation is 5% to 15%. In a large study from the United Kingdom, 49% of obstructions occurred at the splenic flexure, 23% occurred in the left colon, 23% occurred in the right colon, and 7% occurred in the rectum. Obstruction increases the risk of death from CRC 1.4-fold and is an independent covariate in multivariate analyses. Perforation occurs in 6% to 8% of

colorectal carcinoma cases. Perforation increases the risk of death from cancer 3.4-fold.

Pathology

Lower endoscopy with biopsy is often the most efficient method of acquiring tissue for diagnosis. More than 90% of colon cancers are adenocarcinomas. On gross appearance, there are four morphologic variants of adenocarcinoma. Ulcerative adenocarcinoma is the most common configuration seen and is most characteristic of tumors in the descending and sigmoid colon. Exophytic (also known as polypoid or fungating) tumors are most commonly found in the ascending colon, particularly in the cecum. These tumors tend to project into the bowel lumen, and patients often present with a right-sided abdominal mass and anemia. Annular (scirrhous) adenocarcinoma tends to grow circumferentially into the wall of the colon, resulting in the classic apple core lesion seen on barium enema radiologic study. Rarely, a submucosal infiltrative pattern can be observed that is similar to linitis plastica seen with gastric adenocarcinoma. Other epithelial histologic variants of colon cancer that are occasionally seen include mucinous (colloid) carcinoma, signet-ring cell carcinoma, adenosquamous and squamous cell carcinoma (SCC), and undifferentiated carcinoma. Other rare tumors include carcinoids, leiomyosarcomas, and lymphoma. A commonly used grading system is based on the degree of formation of glandular structures, nuclear pleomorphism, and number of mitoses. Grade 1 tumors have the most developed glandular structures with the fewest mitoses, grade 3 is the least differentiated with a high incidence of mitoses, and grade 2 is intermediate between grades 1 and 3.

Staging

Clinical Staging

A thorough history and physical examination should be performed with special attention given to the family history, abdominal, digital rectal and lymph node examinations. Complete evaluation of the lower GI tract with colonoscopy should be performed if not performed at the time of diagnosis. CT colonography can be considered if tumor-related obstruction prevents endoscopic evaluation of the colon proximal to the tumor. National Comprehensive Cancer Network (NCCN) Guidelines Version

2.2016 recommend a CT scan of the chest, abdomen and pelvis, complete blood cell count, CEA and chemistry profile for workup, and clinical staging of colon cancer. For rectal cancer, NCCN recommends the addition of endoscopic rectal ultrasound (ERUS) or pelvic magnetic resonance imaging (MRI). Additionally, we recommend that the operative surgeon perform a proctoscopy him- or herself to accurately determine the distance of the most distal border of the tumor from the anal verge for more accurate preoperative planning. When neoadjuvant therapy is being considered, tattooing the distal edge of the tumor prior to therapy is prudent because a proportion of the patients may experience significant tumor regression or even complete clinical response. Liver function tests (LFTs) are not as useful for determining liver metastasis. Abnormal LFTs are present in only approximately 15% of patients with liver metastases and may be elevated without liver metastases in up to 40%. Preoperative CEA level can reflect the extent of the disease and prognosis: CEA levels surpassing 10 to 20 ng/mL are associated with increased chances of disease failure for both node-negative and node-positive patients. Approximately 18% to 25% of patients will present with stage IV disease at diagnosis. Patient should be inquired for their baseline bowel, urinary, and sexual function. Patients who present with urinary symptoms should undergo evaluation of their urinary tract with preoperative intravenous pyelogram, CT pyelogram, or cystoscopy. At MDACC, CT pyelogram is our initial imaging of choice.

Positron emission tomography (PET) is not routinely indicated in the clinical staging of CRC. However, PET and now PET–CT, are potentially important imaging modalities. The technique uses the glucose analog fluorodeoxyglucose, which accumulates in metabolically active tissues. The standardized uptake value can provide a semi-quantitative determination to help discriminate benign from malignant disease. Although potentially useful in patients presenting with locally recurrent or metastatic disease, it has not been helpful in the primary evaluation of patients with colon cancer due to poor sensitivity, false positives, and high costs.

The clinical staging of rectal cancer warrants more discussion as it has significant therapeutic implications. The decision to proceed with surgery or preoperative multimodality therapy as the first step in treatment of rectal cancer and is based on clinical stage. ERUS is an accurate tool in determining tumor (T) stage. Performed using rigid or flexible probes, the

layers of the rectal wall can be identified with 67% to 93% accuracy. The ERUS characteristics of T1 and T3 tumors make them relatively easy to differentiate. However, the distinction between T2 and T3 tumors is more difficult. ERUS is highly operator-dependent, and it can be difficult to differentiate lymph nodes from blood vessels and other structures or peritumoral edema from tumor. Furthermore, ERUS is limited in its ability to evaluate tumors that are large or bulky or associated with large villous tumors. As a result of these factors, overstaging occurs in approximately 20% of cases and understaging in approximately 10% to 20%. Stenotic lesions may make ERUS impossible secondary to the inability to pass the probe. ERUS evaluation of T stage is superior to that of CT scanning (52% to 83% accuracy) and to rectal MRI (59% to 95% accuracy). Pelvic MRI can additionally delineate the relationship of the tumor to the mesorectal fascia, surrounding viscera, and pelvic structures as well as predict risk for involvement of circumferential margins. The MERCURY Study Group (2006) found that MRI accurately predicted whether surgical margins would be clear or affected by tumor. The relative accuracy of ERUS versus MRI for rectal cancer staging can be operator and institution-dependent. At MDACC, pelvic MRI is the preferred modality for more advanced and bulky disease where circumferential margin assessment is critical, while EUS is the preferred modality for tumors that are anticipated to be of early T stage.

Lymph node staging in rectal cancer has proven more difficult than primary tumor staging, with ERUS accuracies of 62% to 83%, CT accuracies of 35% to 73%, and MRI accuracies of 39% to 84% reported. Despite descriptions of methods to radiologically predict metastases in lymph nodes, only nodal enlargements can be detected with most current technologies. Approximately, 50% to 75% of positive lymph nodes in rectal cancer may be normal in size, thereby limiting accurate evaluation. Similarly, lymph nodes may be enlarged from inflammation, giving false-positive results. Combining size and radiographic characteristics can increase accuracy. For EUS, lymph nodes that are greater than 3 mm and hypoechoic are more likely to contain metastatic deposits. In addition, it is possible to perform fine-needle aspiration of suspicious lymph nodes under ERUS guidance. ERUS or MRI can evaluate lymph node status in patients prior to preoperative therapy, but assessment of response to neoadjuvant therapy can be difficult due to the obliteration of tissue planes by edema and fibrosis secondary to the treatment.

Abdominopelvic CT scanning is important in assessing the presence of distant spread of disease and involvement of adjacent organs. In the management of rectal cancer, it is extremely important to accurately assess the local spread of disease, including the potential involvement of the levator muscles and other pelvic structures. Although ERUS is superior to CT in detecting depth of penetration, CT provides a better assessment of contiguous organ involvement. MRI is a useful adjunct in the evaluation of locally advanced rectal cancer by providing multiple views of the relationships of the tumor to adjacent pelvic structures.

The staging of patients presenting with locally recurrent rectal cancer is complicated by radiation and posttreatment changes that are often difficult to distinguish from tumor. CT is useful to assess the extent of the disease and adjacent organ involvement. In cases where recurrence is unknown but suspected, comparison to prior CT is helpful. Pelvic MRI, rather than EUS, is the imaging modality of choice. It provides detailed anatomic delineation of the extent of the tumor and its relationship to critical pelvic structures, thereby enabling an accurate assessment of resectability. In a selected series, PET has been shown to be up to 95% sensitive, 98% specific, and 96% accurate in the detection of cancer recurrence particularly when the other imaging modalities fail to localize the disease. When used appropriately, it can help distinguish patients who would benefit from surgery for recurrent cancer from those who have unresectable disease, is most useful when images are correlated with those from the MRI. However, further studies are required before this test can be recommended for use on a routine basis. Currently at MDACC, we obtain CT scan of the chest, abdomen and pelvis, MRI of the pelvis, and PET for patients who present with locally recurrent rectal cancer. We believe these studies are complimentary to provide accurate clinical staging, to rule out distant metastatic disease, and to assess local resectability.

Pathologic Staging

British Pathologist Cuthbert Dukes proposed a classification system for colon cancer in 1932. Though the system would go on through several iterations later on, Duke’s efforts highlighted the need to develop a uniform language that could reliably estimate disease burden and portend patient prognosis. The American Joint Committee on Cancer (AJCC) Staging System is currently used to stage CRC. The AJCC published its 7th edition TNM Classification of Colon and Rectum Cancer in 2009. This

system uses a standardized pathologic assessment of depth of tumor penetration (T), extent of regional nodal involvement (N), and the presence absence of metastatic disease (M). A prefix of "c" denotes a clinical classification (cTMN), "p" denotes the pathologic classification (pTMN), and "y" for tumors classified after neoadjuvant therapy (ypTMN). The current AJCC Staging is outlined in Table 12.7. The Astler-Coller Modified Duke staging is sometimes utilized internationally and in the setting of clinical trials. It is detailed in Table 12.8.

TABLE 12.7 TNM Staging Classification of CRC

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues.
T4a	Tumor invades through the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive, or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive but there are tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant Metastases (M)	
M0	No distant metastasis by imaging
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis
M1a	Metastasis confined to one organ or site without peritoneal metastasis
M1b	Metastases to two or more sites or organs without peritoneal metastasis
M1c	Metastasis to the peritoneal surface alone or with other site or organ metastases

Stage	T	N	M	MAC[a]
0	Tis	N0	M0	—
I	T1	N0	M0	A
	T2	N0	M0	B1
IIA	T3	N0	M0	B2
IIB	T4a	N0	M0	B2
IIC	T4b	N0	M0	B3
IIIA	T1–T2	N1/N1c	M0	C1
	T1	N2a	M0	C1
IIIB	T3–T4a	N1/N1c	M0	C2
	T2–T3	N2a	M0	C1/2
	T1–T2	N2b	M0	C1
IIIC	T4a	N2a	M0	C2
	T3–T4a	N2b	M0	C2
	T4b	N1–N2	M0	C3
IVA	Any T	Any N	M1a	—
IVB	Any T	Any N	M1b	—
IVC	Any T	Any N	M1c	—

[a]MAC—Modified Astler-Coller Classification.

TABLE 12.8 Modified Astler–Coller Classification of the Dukes Staging System for CRC

Stage	Description
A	Lesion not penetrating submucosa
B1	Lesion invades but not through the muscularis propria
B2	Lesion through intestinal wall, no adjacent organ involvement
B3	Lesion involves adjacent organs
C1	Lesion B1 invasion depth; regional lymph node metastasis
C2	Lesion B2 invasion depth; regional lymph node metastasis
C3	Lesion B3 invasion depth; regional lymph node metastasis
D	Distant metastatic disease

SURGICAL MANAGEMENT OF COLON CANCER

The goal of primary surgical treatment of colon carcinoma is to eradicate

disease in the colon, the draining nodal basins, and contiguous involved organs. Careful surgical planning is essential. The stage of disease, presence of synchronous colonic tumors, and the presence of underlying CRC syndromes are significant factors in determining the optimal surgical approach. The patient's general medical condition is also important because most perioperative deaths result from cardiovascular or pulmonary complications.

Anatomy

Thorough knowledge of the arterial, venous and lymphatic anatomy of the colon and rectum is essential for appropriate surgical management (Fig. 12.3). The cecum, ascending and proximal transverse colons are embryologically derived from the midgut and receive their arterial blood supply from the superior mesenteric artery via the ileocolic, right, and middle colic arteries. The distal transverse, descending, and sigmoid colon are hindgut derivatives whose arterial blood supply arises from the inferior mesenteric artery (IMA) through the left colic and sigmoid arteries. The rectum, also a hindgut derivative, receives its blood supply to the upper third from the IMA via the superior hemorrhoidal artery. The middle and lower thirds of the rectum are supplied by the middle and inferior hemorrhoidal arteries, which are branches of the hypogastric artery. Collateral blood supply for the colon is provided through the marginal artery of Drummond and the arc of Riolan. The venous drainage of the colon and rectum parallels the arterial supply, with the majority draining directly into the portal venous system. This provides a direct route for metastatic spread of tumor to the liver. The only minor anatomical variation in the venous drainage compared with the arterial supply is that the inferior mesenteric vein (IMV) joins the splenic vein before emptying into the portal system. The rectum has dual venous drainage; the upper rectum drains into the portal system, and the distal one-third of the rectum drains into the inferior vena cava via the middle and inferior hemorrhoidal veins, providing a direct route for hematogenous spread outside the abdomen.

The lymphatic drainage of the bowel is more complex than the vascular supply. Lymphatics begin in the bowel wall as a plexus beneath the lamina propria and drain into the submucosal and intramuscular lymphatics. The epicolic lymph nodes drain the subserosa and are located in the colon wall. This nodal group runs along the inner bowel margin between the intestinal

wall and the arterial arcades. These nodes in turn drain into the paracolic nodes, which follow the routes of the marginal arteries. The epicolic and paracolic nodes represent the majority of the colonic lymph nodes and are the most likely sites of regional metastatic disease. The paracolic nodes drain into the intermediate nodes, which follow the main colic vessels. Finally, the intermediate nodes drain into the principal nodes, which begin at the origins of the superior and inferior mesenteric arteries and are contiguous with the para-aortic chain.

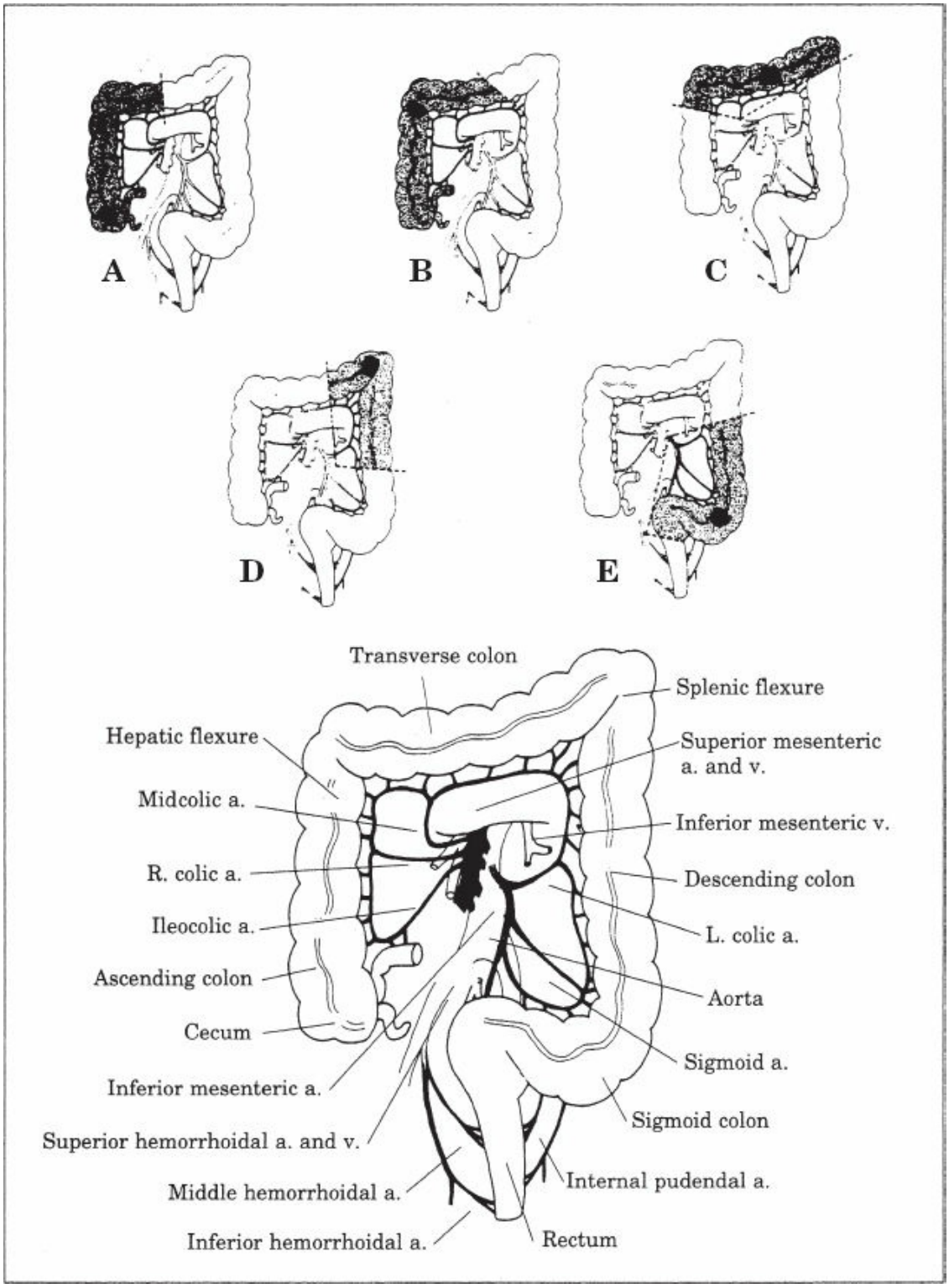

Figure 12.3 Anatomy of colonic blood supply along with a pictorial description of the various anatomical resections used for colon carcinoma. **A:** Right hemicolectomy. **B:** Extended right hemicolectomy. **C:** Transverse colectomy. **D:** Left hemicolectomy. **E:** Low anterior resection. (From Sugarbaker PH, MacDonald J, Gunderson L. CRC. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of*

Oncology. 3rd ed. Philadelphia, PA: Lippincott; 1984, with permission.)

The route of lymphatic flow parallels the arterial and venous distribution of the colon. The right colon will drain to the superior mesenteric nodes through the intermediate nodes or to the portal system via the lymphatics of the superior mesenteric vein. The left colon's lymphatic drainage follows the marginal artery to the left colic intermediate nodes and finally to the inferior mesenteric nodes. The lymphatic drainage of the upper third of the rectum follows the IMV, whereas the lower two-thirds drain into the hypogastric nodes, which, in turn, drain into the para-aortic nodes. The lower third of the rectum can also drain along the pudendal vessels to the inguinal nodes.

Surgical Options

Curative-intent surgical resection should be conducted anatomically based on the location of the tumor and the corresponding arterial supply and lymphatic drainage. At resection, the primary tumor and its lymphatic, venous, and arterial supply are extirpated taking care to perform a high ligation of appropriate vessels. If there is contiguous organ involvement, those organs are removed en bloc with the tumor, aiming for microscopically negative margins (R0).

Right Hemicolectomy

This operation involves removal of a portion of the distal ileum, right colon, hepatic flexure, and transverse colon just proximal to the middle colic artery. The ileocolic, right colic, and right branch of the middle colic vessels are ligated at their takeoffs from the central mesenteric vessels. This procedure is indicated for cecal and ascending colonic lesions. Major morbidities include ureteral injury, duodenal injury, and rarely bile acid deficiency. Anastomotic dehiscence is a risk with all bowel resections that include reconstruction.

Extended Right Hemicolectomy

This procedure includes resection of the transverse colon (including ligation of the entire middle colic artery at its origin) in addition to the structures removed in the right hemicolectomy. It generally requires mobilization of the splenic flexure to allow a tension-free anastomosis.

Indications for the procedure are hepatic flexure or transverse colon lesions. Morbidities include splenic injury in addition to those associated with right hemicolectomy. Ninety percent of the fecal water is absorbed in the proximal colon; therefore, extended resections are associated with the potential for diarrhea.

Transverse Colectomy

This procedure involves the segmental resection of the transverse colon. There is controversy as to the oncologic appropriateness of transverse colectomy for mid transverse colon cancer, and often extended right or extended left hemicolectomy is preferred over segmental transverse colectomy. However, this procedure may be preferred in select patients who are elderly, infirm, or in whom the surgeon wishes to minimize the risk of postoperative diarrhea. To prevent anastomotic dehiscence, a well-vascularized and tension-free anastomosis is mandated. This requires mobilization of both the right and the left colons, along with both flexures with an ascending-to-descending colon anastomosis.

Left Hemicolectomy

This resection involves the removal of the transverse colon distal to the right branch of the middle colic artery and the descending colon up to, but not including, the rectum. The left branch of the middle colic, and either the IMA or its branches up to the left colic vessels, are ligated. This operation may be tailored to the location of the lesion. Indications for the procedure are left colon and splenic flexure lesions. Morbidities include splenic and ureteral injury.

Low Anterior Resection

When performed for lesions of the distal sigmoid colon or proximal rectum, this procedure includes removal of the sigmoid colon and a portion of the rectum. The arterial ligation should be performed at the highest level on the superior rectal artery as a minimum, when no clinically suspicious nodes are present above this level. Ligation should occur at the level of the proximal IMA when central lymphadenectomy is needed and when necessary to achieve a tension-free anastomosis. The splenic flexure is routinely mobilized and the reconstruction is performed using the descending colon. The use of the sigmoid colon is discouraged, especially for distal reconstruction as the thickened and hypertrophic muscle of the

sigmoid is less compliant and less well vascularized than the descending colon. The IMV can be ligated at the inferior border of the pancreas to gain additional length in order to insure a tension-free anastomosis. For lesions involving the rectum, the mesorectum should be divided at least 5 cm distal to the distal aspect of the tumor. A 2 cm distal margin is acceptable only for rectal cancers arising from within 5 cm of the anal verge. Morbidities include anastomotic dehiscence, which is higher with more distal reconstruction and approaches 10%, and bowel ischemia (secondary to inadequate flow through the marginal artery of Drummond). For routine low anterior resections (LARs) for sigmoid or upper rectal lesions without radiation, a defunctioning ileostomy is not typically necessary.

Total Abdominal Colectomy

This resection involves the removal of the entire colon to the rectum with an IRA. Subtotal colectomy refers to removal of nearly the entire colon with an anastomosis above the rectum. These procedures are typically indicated for multiple synchronous colonic tumors arising in different anatomic regions, for selected patients with FAP with rectal sparing, and for selected patients with colon cancer in the setting of HNPCC. Although an excellent quality of life can be achieved after ileorectostomy, frequent loose bowel movements are the norm. Patients should be counseled regarding a bowel regimen and perianal care. The risk for anastomotic leak after IRA is approximately 5% or less.

The surgical treatment of the familial polyposis syndromes depends on the age of the patient and the polyp density in the rectum. Surgical options include total proctocolectomy with end ileostomy, total abdominal colectomy with IRA, or restorative proctocolectomy with ileal pouch anal anastomosis (IPAA). Total abdominal colectomy with IRA has a low complication rate, provides good functional results, and is a viable option for patients with low rectal adenoma burden (e.g., fewer than 20 adenomas). These patients must be followed postoperatively with 6- to 12-month endoscopic examinations for adenoma clearance. If rectal polyps become too numerous or undergo malignant transformation, completion proctectomy is warranted. Restorative proctocolectomy with IPAA has the advantage of removing all, or nearly all, colorectal mucosa at risk for cancer while preserving transanal defecation. Complication rates are low when this procedure is done in large centers. Morbidity from the procedure

includes incontinence, multiple loose stools, impotence, retrograde ejaculation, dyspareunia, and pouchitis. Approximately 7% of patients have to be converted to permanent ileostomy due to complications after the procedure. The Cleveland Clinic Foundation recently evaluated their registry of patients with FAP who were treated with IRA or IPAA. Prior to the use of IPAA for patients with high rectal polyp burdens, the risk of cancer in the retained rectum was 12.9% at a median follow-up of 212 months. Because of the use of IPAA for patients with large rectal polyp burdens and the selected use of IRA for those with low rectal polyp burdens, no patient has developed rectal cancer in the remaining rectum at a median follow-up of 60 months.

Obstructing CRCs

Obstructing or perforated left-sided CRCs are usually treated in two stages: resection and Hartmann procedure, followed by restoration of gastrointestinal continuity. Contraindications for primary anastomosis include advanced peritonitis, hemodynamic instability, poor general health, steroid therapy, or immunosuppressed state. An alternative is a one-stage procedure with either subtotal colectomy and primary anastomosis or a segmental resection and intraoperative colonic lavage for carefully selected patients. The main concerns about lavage include increased operative time, contamination and spillage, and need for additional equipment and expertise.

In the SCOTIA prospective randomized trial, comparing these two treatment modalities in 91 patients with malignant left-sided colonic obstruction, the morbidity and mortality rates were similar. Endoscopic stenting of obstructive lesions can be used as a bridge therapy to allow for bowel preparation and subsequent single-step resection. Obstructing right-sided cancers can be effectively treated with resection and anastomosis in one stage.

Treatment of Locally Advanced Colon Cancer

Colon cancers that extend into adjacent structures have up to a 53% chance of local failure after complete resection. Approximately 10% of carcinomas present in this fashion. Strategies designed to reduce local recurrence by removing the tumor en bloc without violation must be elucidated prior to the operating room and depend heavily on preoperative imaging and planning. Resection of CRC that has invaded adjacent

structures involves en bloc resection of all involved structures; failure to do so results in significantly increased local recurrence and decreased survival. Importantly, all adhesions between the carcinoma and adjacent structures should be assumed to be malignant and not taken down. Thirty-three to 84% of these adhesions are found to be malignant when examined histologically. The affected organ should have resection limited to the involved area with a margin of normal tissue. A patient who has a margin-negative multivisceral resection has a chance of attaining the same survival as a patient with no adjacent organ involvement on a stage-matched basis.

Retrospective series have shown subsets of patients who have benefited from postoperative radiation therapy with or without 5-FU–based chemotherapy. Unfortunately, there are no consistent criteria to use in assessing increased risk of local failure. The value of adjuvant radiation therapy after complete resection of high-risk colon cancer is currently being evaluated in a randomized prospective fashion (NCCTG 91-46-52). In this trial, patients with B3 or C3 (modified Astler-Coller) tumors are randomized to receive postoperative 5-FU/levamisole or 5-FU/levamisole and radiation therapy. Patients with incompletely resected cancers fare worse than those with positive microscopic disease, as one would expect. It has been found that radiation therapy is more effective in treating microscopic than macroscopic disease and that it is more effective when combined with 5-FU. In a recent retrospective Mayo Clinic study of 103 mostly stage B3 and C3 (modified Astler-Coller) patients, in which 49% had no residual disease, 17% had microscopic residual disease, and 34% had gross residual disease; the local failure rate was 10% for patients with no residual disease, 54% for those with microscopic residual disease, and 79% for those with gross residual disease. More recently, improved local control with adjuvant radiation has been demonstrated in a small set of patients with T4 cancers with perforation or fistula. However, the incremental benefit of adjuvant radiation for local control must be carefully deliberated against potential injury to nearby organs and long-term adverse effects of radiation.

Survival

Five-year overall and disease-free survival (DFS) of patients with colon cancer varies with pathologic stage. Nodal involvement is the primary determinant of OS. In node-negative disease, the 5-year survival rate is 90% for patients with T1 and T2 lesions and 80% for those with T3

lesions. For node-positive cancers, the 5-year survival ranges from 74% with N1 disease to 51% with N2 disease. These figures also vary depending on the total number of lymph nodes retrieved and evaluated in the surgical specimen, with improved survival associated with a higher number of lymph nodes evaluated. Other factors that are proven prognostic indicators include grade, bowel perforation, and obstruction. Patients who present with unresectable metastatic disease have poor OS with 5-year survival at 11%. In patients who undergo resection of distant metastasis, 5-year survival approaches 40% in some series.

Adjuvant Therapy

Most patients with colon cancer present with disease that appears localized and can be completely resected with surgery. However, almost 33% of patients undergoing curative resection will relapse with recurrent disease secondary to unresected occult microscopic metastasis. Adjuvant therapy is administered to treat and hopefully eradicate this residual micrometastatic disease. Adjuvant systemic therapy is recommended for all patients with stage III disease where their risk of recurrence approaches 50%. However, the role of adjuvant therapy in stage II CRC is more controversial. Approximately 20% of patients with resected stage II colon cancer will recur. Several adjuvant trials included both stage II and III diseases. Subgroup analysis of stage II patients in the NSABP C-07 and MOSAIC trials showed trends toward benefit without reaching statistical significance, as these trials were underpowered to see a difference in this subgroup. However, three meta-analyses from the NSABP, NCCTG, and International Multi-Center Pooled Analysis of Colon Cancer Trials suggest only marginal improvements in disease-free and OS with 5-FU and LV in stage II colon cancer patients. Adjuvant chemotherapy in stage II patients provides a relative improvement in overall 5-year survival that was comparable to that seen in stage III patients (approximately 30% relative improvement). However, the absolute improvement in OS is only 2% to 7%. Multi-gene testing platforms for recurrence risk stratification have shown more robust utility in breast cancer than colon cancer, where they have not been able to deliver added prognostic or predictive power to guide the choice of chemotherapy agents. Current recommendations reserve adjuvant chemotherapy for high-risk stage II colon cancers, which are defined by T4 lesions, <12 harvested lymph nodes, lymphovascular invasion, bowel obstruction or bowel perforation, and poorly differentiated

histology.

SURGICAL MANAGEMENT OF RECTAL CANCER

The rectum can be generally divided into thirds: lower, middle, and upper. The upper rectum extends above 12 cm from the anal verge however, the length of the rectum varies significantly depending on the size of the individual, and therefore these distinctions should be individualized. Tumors of the upper rectum, at the level of the sacral promontory are labeled “rectosigmoid” because they can behave similarly to colon cancers. Their surgical management is analogous to the management of colon cancer previously discussed. The remainder of this discussion will outline the management of rectal cancer within 12 cm of the anal verge.

The primary goal of rectal cancer surgery is to achieve a negative margin resection of the primary tumor with resection of all draining lymph nodes. Additional goals include restoration of intestinal continuity and preservation of anorectal sphincter, sexual, and urinary function when possible. Achieving these targets can be difficult due to the anatomical constraints of the bony pelvis. There is also significant surgeon- and center-related variation in patient outcomes after treatment for rectal cancer. The Stockholm Rectal Cancer Study Group found that specialists and high-volume centers had lower local failure rates and improved survival rates when compared to low-volume practitioners. As such, it is not unusual to see wide ranges of local recurrence rates from 3.7% to 43% in various series for curative surgical resection, with or without multimodal therapy.

Clinical Staging

At the time of diagnosis, all rectal cancer patients should undergo total colonoscopy to assess for synchronous tumors. Surgeons should perform proctoscopy at initial evaluation to confirm location of the tumor from the anal verge as well as the anorectal ring which is the top of the anal sphincters. A CT of the chest, abdomen and pelvis should be performed and baseline CEA levels acquired. Assessment of clinical T and N stage can be performed using MRI or ERUS. Meta-analysis of studies investigating the accuracy of CT, MRI, or ERUS for preoperative staging in rectal cancer show MRI and ERUS with similar T stage sensitivity, with a slight increase in specificity with ERUS. MRI and ERUS have

equivalent sensitivity for N stage, but only MRI provides excellent assessment of the circumferential margin. For this reason, high-resolution MRI is the preferred modality for clinical rectal cancer staging.

Preoperative Versus Postoperative Radiation Therapy

Several advantages to the use of preoperative compared with postoperative radiation therapy have been identified, including the following:

1. There is a decreased risk of local failure due to improved compliance with the chemoradiation regimen and improved tumor response in the preoperative setting. There is a decreased risk of toxicity because the small bowel can more readily be excluded from the radiation field in a preoperative setting.
2. There is less bowel dysfunction because the colon used for reconstruction is not in the radiation field.
3. A reduction in tumor size increases rates of sphincter preservation in those patients initially deemed to require APR and improves overall resectability.
4. There is no delay of therapy as in some cases of postoperative therapy due to operative morbidity.

Several randomized trials evaluating the role of preoperative radiation therapy in resectable rectal cancer report significant decreases in local recurrence. The German Rectal Cancer Study Group (CAO/ARO/AIO-94) demonstrated a significant reduction in local recurrence and radiation related toxicity in stage II/III rectal patients undergoing preoperative radiation versus postoperative chemoradiation. Though there was no difference in OS or DFS between groups; the difference in local recurrence persisted at 10-year follow-up. The Swedish Rectal Cancer Trial randomized stage I/II/III rectal cancer patient to surgery alone versus preoperative short course radiation (25 Gy in 5 days) followed by surgery. At 13-year follow-up, they demonstrated persistent improved local recurrence rate, DFS, and OS in the preoperative radiation arm. The findings support the recommendation for preoperative radiation in patients with high risk (T ≥3, node positive) rectal cancers.

In the United States, preoperative radiation therapy trials have usually included chemotherapy in a more protracted course rather than using short-course radiotherapy alone. Concurrent chemotherapy with long-course radiation has two benefits. Chemotherapy primarily serves as a sensitizer to radiation, aiding its delivery and effectiveness. A Cochrane systematic

review of stage III rectal cancer patients randomized to preoperative concurrent chemoradiation versus radiation only showed a decrease in local recurrence in the patients receiving chemoradiation without a difference in OS. Other studies have shown that concurrent preoperative chemoradiation is more likely to exhibit significant reduction in tumor size and achieve pathologic complete response (pathCR) when compared to preoperative radiation only.

The complications associated with chemoradiation treatment include radiation enteritis and dermatitis, autonomic neuropathy, hematologic toxicity, stomatitis (mostly with continuous 5-FU infusions), and venous access infections. The frequency and intensity of these complications depend on multiple factors, including radiation therapy total dosing, fractionation, field technique, and whether the radiation therapy is given preoperatively or postoperatively. There are no good predictors of which patients will have these complications and to what degree they will have them.

Resection Margins

Low rectal cancers are at an increased risk for positive proximal, distal, and especially circumferential resection margins (CRMs). In 1986, Quirke et al. were the first to characterize the critical importance of the negative radial margin in preventing rectal cancer recurrence. In their series, the rate of local recurrence was 86% in the setting of a positive radial resection margin. The proximal margin is rarely a problem in rectal cancer. In low rectal cancers however, the distal and circumferential margins require good judgment and technique. Histologic examination of the bowel wall distal to grossly resected rectal cancers show that only 2.5% of patients will have submucosal spread of disease greater than 2.5 cm.

It has been well documented that negative radial margins are major determinants of local recurrence and survival. Radial margin clearance can be maximized by sharp dissection between the fascia propria of the mesorectum and the endopelvic fascia. Positive CRM typically is due to an incomplete total mesorectal excision (TME) from medial violation of the mesorectal envelope and disruption of the mesorectum. TME involves sharp excision and extirpation of the mesorectum by dissecting outside the investing fascia of the mesorectum. During an abdominal perineal resection (APR), however, the last portion of the rectum just above the anorectal ring that abuts the levator muscle should not be dissected in a

“coning” in fashion, but rather, a cylindrical approach should be undertaken (Fig. 12.4). The cylindrical approach requires a standard TME to the level of the levators and a wide extralevator resection. It has been shown to improve oncologic outcomes by reducing CRM positivity in patients with low anorectal cancers. At MDACC, tumor-specific TME is performed for cases where restoration of GI continuity is anticipated. This would include the entire mesorectum for the lower and lower-middle rectal cancers, while preserving a portion of the mesorectum for upper and upper-middle rectal cancers. The mesorectum is transected 5 cm distal to the distal aspect of the tumor arising in the mid to upper rectum. A distal margin of 2 cm is the aim for low-lying tumors. Shorter distances can be considered in individual cases particularly with a demonstrated excellent response to preoperative neoadjuvant therapy in this location. This tumor-specific mesorectal excision does not compromise an adequate oncologic operation and may decrease the risk for anastomotic dehiscence from devascularization of the rectum. Disease-related contraindications for sphincter preservation include involvement of the anal sphincter complex and/or the levator ani muscle. For abdominoperineal resections, TME with a cylindrical approach is performed.

Lymphadenectomy

Adequate lymphadenectomy should be performed for accurate staging and local control. Proximal vascular ligation at the origin of the superior rectal vessels from the IMA should be considered a minimum standard. High ligation of the IMA at its takeoff from the aorta has been advocated for complete lymphadenectomy, although its oncologic value remains controversial. High ligation of the IMA should be performed when clinically suspicious nodes are present and/or when additional reach is needed for the colonic conduit. Nodal spread from the primary tumor occurs along the mesorectum. Therefore, the mesorectal margin should be at least 5 cm distal to the inferior aspect of the tumor or to the end of the mesorectum at the pelvic floor. The technique of TME provides adequate lymphadenectomy for most rectal cancers. TME optimizes the oncologic operation by not only removing draining lymph nodes but also maximizing lateral resection margins around the tumor. There is overwhelmingly comparative observational evidence that demonstrates a significant decrease in the local recurrence rate (in the range of 6.3% to 7.3%) compared with conventional surgery (15% to 30%).

Ligation of the IMA, with or without parallel ligation of the IMV at or near its origin (“high ligation”) allows for maximal mobilization of the proximal bowel to facilitate a tension-free low pelvic or coloanal anastomosis (CAA). Lateral pelvic lymphadenectomy is controversial. No benefit in survival or local disease control has been attainable with the use of more extended lateral lymphadenectomy (iliac and obturator nodes), and the complication rates are higher with these more extensive surgical procedures. At MDACC, it is performed when clinically suspicious nodes are present.

A

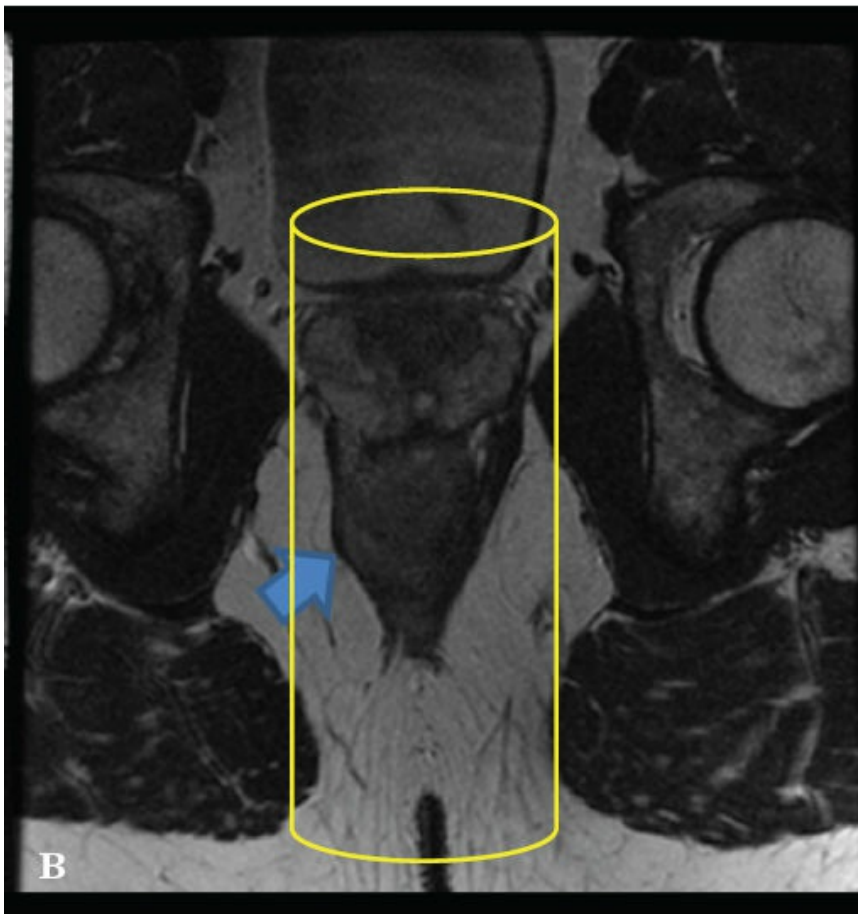
B

Figure 12.4 **A:** Failure of the total mesorectal excision plane for low rectal cancers. **B:** Cylindrical approach to total mesorectal excision.

Surgical Approaches to Rectal Cancer

Surgical approaches to the rectum include transabdominal procedures (LAR, CAA, APR), transanal approaches (local excision, LE), and transsacral approaches (York-Mason, Kraske). The latter two approaches will be discussed in detail in the section Local Approaches to Rectal Cancer. Historically, APR, an operation devised by Ernest Miles in the 1930s, was the treatment for all rectal cancers. With the advent of better preoperative staging, neoadjuvant therapy, and improved surgical techniques and stapler technology, the use of APR has decreased significantly. APR is now reserved for patients with primary sphincter dysfunction and incontinence, patients with direct tumor invasion into the sphincter complex or levator ani, and patients with large or poorly differentiated lesions in the lower third of the rectum that do not have adequate tumor clearance for sphincter preservation.

Sphincter Preservation Procedures

Besides local excision, sphincter preservation procedures include LAR and proctectomy/CAA. Gastrointestinal continuity can be restored with a direct end-to-end anastomosis; sometimes the addition of a colonic reservoir is considered for improved short-term function. Sphincter preservation should only be performed if the oncologic result is not compromised and the functional results are anticipated to be acceptable. It was demonstrated more than 20 years ago that there is no difference in local recurrence rate or survival in patients with midrectal cancers who undergo LAR rather than APR. The technical feasibility of LAR in this setting was increased with the advent of circular stapling devices and the knowledge that distal mucosal margins of resection of 2 cm were adequate in the setting of TME. An alternative to LAR is proctectomy with CAA. It is used in low rectal cancers, with the stapled or hand-sewn anastomosis just above or at the dentate line. Temporary fecal diversion is routinely performed. Using either LAR or proctectomy with CAA (and adjuvant therapy), MDACC and others have reported recurrence rates of 5.3% to 7.9%. Functional results have been good, with 60% to 86% of patients attaining continence

by 1 year, 10% to 15% requiring laxative use, and some patients with mild soiling at night. Preoperative chemoradiation does not seem to have a negative impact on these functional results. The lower the anastomosis the greater the potential for bowel dysfunction. Many patient factors are related to the decision to avoid a colostomy; however, there have been no randomized comparative studies of quality of life after CAA versus APR.

Colonic J Pouch

Although continence can be maintained in patients with CAA, there is a degree of incontinence in some patients, and many require antidiarrheal agents. This is partly due to the lack of a compliant reservoir after proctectomy. This led to the introduction of the colonic J pouch for low rectal cancers that resulted in better outcomes in terms of stool frequency, urgency, nocturnal bowel movements, and continence compared to straight coloanal anastomoses. These advantages are principally during the first 12 to 24 months after which time the function of al improvements after straight anastomosis improves. One potential problem, especially when the pouch is longer than 5 or 6 cm, is difficulty in pouch evacuation (approximately 20% of patients). As in anterior resection, the functional outcome of patients with CAA (with or without a J pouch) may take 1 to 3 years to stabilize and is related to the level of the anastomosis (lower anastomoses tend to have poorer function). Unfortunately, many, particularly male patients with low rectal cancers, do not have enough room within the pelvis to accommodate a colonic J pouch. An alternative approach of a transverse coloplasty pouch has been proposed but it has not been shown to demonstrate significant benefit over a straight anastomosis. Postoperative radiation therapy has not been shown to have a significant adverse effect on pouch function.

Proximal Diversion

Proximal diversion after sphincter preservation is generally performed in the following circumstances: (a) anastomosis less than 5 cm above the anal verge, (b) patients who have received preoperative radiation therapy, (c) patients on corticosteroids, (d) when the integrity of the anastomosis is in question, and (e) any case of intraoperative hemodynamic instability.

Local Approaches to Rectal Cancer

Local treatment alone as definitive therapy of rectal cancer was first

applied to patients with severe coexisting medical conditions unable to tolerate radical surgery. Currently, local approaches are being more widely considered and have the benefits of potentially sparing major perioperative risks and obtaining favorable functional results. Local excision has been associated with up to 97% local control rate and 92% disease-specific survival for properly selected individuals with early cancers. Local treatment is best applied to rectal cancers within 10 cm of the anal verge, less than 3 cm in diameter involving less than one-third of the circumference of the rectal wall, tumors staged as T1 by EUS, highly mobile and of low histologic grade. The decision to use local excision (with negative margins) alone or to employ adjuvant therapy after local excision is based on the pathologic characteristics of the primary cancer and the potential for micrometastases in the draining lymph nodes. T1 lesions have been associated with positive lymph nodes in up to 18% of cases, whereas the rate for T2 and T3 lesions is up to 38% and 70%, respectively. T2 tumors treated with local resection alone have local recurrence rates of 25% to 62%. Local excision alone is not considered adequate therapy for T1 lesions with poor prognostic features and all T2 tumors. However, when local excision is performed due to medical comorbidities, neoadjuvant or adjuvant chemoradiation and close surveillance should also be considered. Two phase II cooperative group studies evaluated local excision for T1 lesions and local excision with adjuvant chemoradiation using a 5-FU–based regimen for T2 lesions. The CALGB 8984 trial evaluated 177 patients who underwent transanal excision for T1 or T2 lesions. T2 patients were given adjuvant chemoradiation and T1 patients were followed for recurrence and survival. At a median follow-up of 7.1 years, 4 of 59 patients with T1 lesions (2 local, 1 local and distant, and 1 distant) and 10 of 51 patients with T2 lesions (5 local, 2 local and distant, and 3 distant) had recurrences. OS rates were 84% and 66% and DFS 75% and 64%, respectively. Local recurrence rates for patients with T1 and T2 lesions were 8% and 18%, respectively. The Radiation Therapy Oncology Group (RTOG) protocol 89–02 used a similar strategy with a median follow-up of 6.1 years in 52 patients with T1/T2 rectal cancers and demonstrated a 4% local failure rate for T1 lesions and 16% local failure rate for T2 lesions. An additional 3 of 13 (23%) patients with T3 disease treated with local excision and chemoradiation were noted to have local failure. These data should be considered in the background of data from other studies demonstrating a

recurrence rate of 18% and 37% in patients undergoing local excision alone for T1 and T2 tumors, respectively. The ACOSOG Z6041 trial is a phase II trial of neoadjuvant chemoradiation (capecitabine, oxaliplatin, and radiation) followed by local excision for uT2N0 rectal cancers. The primary end-point was 3-year DFS, which was 88.2% among 79 patients after a median follow-up of 56 months.

Transanal excision is the conventional approach to removing distal rectal cancers. In order to ensure a full-thickness excision, the deep plane of dissection is the perirectal fat. Tumors should be excised in a nonpiecemeal fashion, with a 1 cm circumferential margin.

Transanal endoscopic microsurgery (TEM) provides accessibility to tumors of the middle and upper rectum, which would otherwise require a laparotomy or transsacral approach, through improved visibility and instrumentation. This approach can be used for selected lesions up to 15 cm from the anal verge. Caution must be taken with higher lesions because full-thickness excision can result in perforation into the abdominal cavity that will result in intraoperative leakage of gas and potential for injury to intraperitoneal organs. The procedure is technically demanding and requires special equipment and is not recommended for tumors within 5 cm of the anal verge.

Other local approaches are mentioned here for historical interest and are rarely performed in clinical practice today. *Posterior proctotomy* involves a posterior incision along the paracoccygeal plane above the anus (Kraske procedure) or to the anus (York-Mason procedure), the coccyx is removed, and the levator is divided. The rectum can then be mobilized for a sleeve resection, or a proctotomy is performed for excision of the tumor. This procedure presently has limited application for rectal tumors.

Fulguration uses either standard electrocautery or laser to ablate the tumor. *Endocavitary radiation* is a high-dose, low-voltage irradiation technique that applies contact radiation to a small rectal cancer through a special proctoscope. Fulguration and endocavitary radiation are used for palliation.

Patient selection for local procedures is important, and it is recommended that patients have preoperative EUS to accurately identify T stage and to select superficial lesions. Patients with deeper lesions could only be considered potential candidates if there is concurrent metastatic disease or significant comorbid conditions. Although local procedures have become more commonly used, few randomized prospective trials

have evaluated oncologic and functional outcomes compared with anterior resection or APR. In 1996, Winde et al. prospectively randomized 50 patients with T1 adenocarcinoma of the rectum to either anterior resection or TEM. Similar local recurrence and survival rates, as well as decreased morbidity rates for local excision, were found in the two study arms.

At MDACC, transanal local excision is used for highly selected early T1 tumors with favorable features, while radical resection is preferred for other rectal lesions. Optimal specimens from local excision are characterized by nonpiecemeal full-thickness excision, at least a 1-cm mucosal margin circumferentially, and are not fragmented. An inadequate local excision mandates an alternate resection strategy, not merely the addition of adjuvant therapy. If preoperative T stage is increased after pathologic evaluation following local excision, the appropriate standard resection is recommended. T1 tumors with any poor prognostic features identified (e.g., tumor greater than 4 cm, poorly differentiated histologic type, lymphatic or vascular invasion, or clinical or radiologic evidence of enlarged lymph nodes) are not appropriate for local excision. For patients with T2 tumors, local excision should only be considered when radical resection is contraindicated and should be performed in conjunction with neoadjuvant or adjuvant therapies ideally in the context of a clinical protocol. Finally, T3 lesions are considered for local excision alone only if radical resection is contraindicated or if the patient refuses a radical procedure.

Treatment of Locally Invasive Rectal Cancer

Approximately 10% of rectal cancer patients will present with involvement of adjacent structures (bladder, vagina, ureters, seminal vesicles, and sacrum). Locally invasive rectal cancers are historically difficult to treat. Recurrence rates can be high with surgery alone, but outcomes have significantly improved with the use of multimodality treatment. Although preoperative and adjuvant therapy is important in these patients, the mainstay treatment in rectal cancer is R0 resection of the tumor with complete TME and en bloc resection of involved structures. The confines of the pelvis and the proximity of critical nerves and blood vessels are frequent challenges. Intraoperative radiation therapy (IORT) or brachytherapy has been shown to provide additional potential benefit.

Improved resectability and decreased locoregional recurrence have been demonstrated for locally invasive rectal cancers after preoperative

chemoradiation treatment. As reported by the Mayo Clinic, the addition of IORT to standard external-beam radiation therapy with 5-FU in patients with locally invasive rectal cancer has been associated with improved local disease control and possibly some improvement in survival. Preoperative chemoradiation has also been shown to improve rates of sphincter preservation in patients who were initially believed to need APR for curative resection by as much as twofold when compared with postoperative chemoradiation regimens. The best chance of cure in patients with locally invasive disease appears to involve preoperative chemoradiation treatment, maximal surgical resection, with IORT used in selected cases.

At MDACC preoperative chemoradiation is standard treatment for locally invasive rectal cancer. Patients undergoing R0 pelvic exenteration for local disease control have demonstrated that the addition of chemoradiation may significantly improve survival, and that chemoradiation response and S-phase fraction were important determinants of OS. Patients with low-risk factors had a 65% 5-year survival, whereas high-risk patients had only a 20% survival.

Laparoscopic and Robotic Approaches to CRC

Studies have confirmed that laparoscopic colectomy for colon cancer is technically feasible and safe, yielding an equivalent number of resected lymph nodes and length of resected bowel when compared with open colectomy. Early concerns regarding port-site metastases have been largely addressed due to its rarity. A number of landmark-randomized trials have demonstrated oncologic noninferiority of laparoscopic versus open surgery for colon cancer.

The National Cancer Institute–sponsored multicenter clinical outcomes of surgical therapy (COST) trial enrolled nearly 800 patients and validated the oncologic safety and equivalency of laparoscopy for colon cancer with the exceptions of transverse colon cancer and T4 disease. Laparoscopic-assisted colectomy for cancer was associated with equivalent recurrence-free and OS when compared with open surgery with no increase in wound recurrences. Statistically significant patient-related benefits included reduced length of hospital stay (1 day shorter in the laparoscopic group, 5 vs. 6 days, $P < 0.001$) and decreased pain (1 day less each of parenteral narcotics [3 vs. 4 days, $P < 0.001$] and oral analgesics [1 vs. 2 days, $P = 0.02$]). There was a small improvement in short-term quality of life, and a

small benefit in long-term quality of life could be documented for the patients treated with laparoscopic resection.

In rectal cancer however, laparoscopic resection has had mixed results. The colon carcinoma laparoscopic or open resection (COLOR) II trial included a subgroup of patients with rectal cancer who were randomized to laparoscopic versus open surgery for rectal cancer. The primary endpoints were locoregional recurrence rates at 3 years and secondary endpoints included overall and DFS. Laparoscopic surgery in patients with rectal cancer was associated with rates of locoregional recurrence and disease-free and OS similar to those for open surgery. ACOSOG Z6051 was a phase III randomized controlled trial with a noninferiority design and 1:1 randomization of laparoscopic versus open rectal resection. Primary endpoints included CRM, distal margins, number of lymph nodes recovered, and integrity of the mesorectum. Secondary endpoints included DFS and local recurrence at 2 years. This trial failed to meet the criterion for noninferiority in terms of short-term primary endpoints.

Minimally invasive techniques result in faster recovery, and have the putative benefits of improved quality of life and lower overall health care costs when compared with open laparotomy. When considering colectomy, reduction in postoperative pain and narcotic use, faster resolution of ileus, and shorter duration of hospitalization are unifying observations of the laparoscopic approach. Added benefits may include the potential for improved short- and long-term complications and a reduction in costs. Further investigation will be required to determine whether the small statistical benefits that have been seen in the randomized clinical trials are clinically significant as well. Furthermore, the importance of these effects may in part depend on the underlying diagnosis. Most patients with colon cancer are candidates for laparoscopic-assisted techniques. Transverse colon tumors require extensive bilateral colonic mobilization and therefore are technically more difficult. Factors associated with an increased need for conversion include tumor-related factors such as proximal left-sided lesions and large bulky tumors, as well as patient obesity, adhesions, and the presence of an associated abscess that was not preoperatively identified. Cancers with perforation, obstruction, or invasion of the retroperitoneum or abdominal wall are not approached laparoscopically.

Since its introduction, the robotic interface has rapidly gained acceptance among colorectal surgeons. Its improved dexterity, range of motion, and better visualization offer significant advantages over

laparoscopy and are of particular interest in rectal surgery. Most studies have focused on elucidating the clinical benefits of robotic rectal cancer surgery. However, no clear advantage has been shown to support any one technology over the other. One meta-analysis of the current study suggests that the robotic interface may offer a lower conversion rate, better TME, and earlier recovery of voiding and sexual function over laparoscopic rectal surgery. While these results are positive, more rigorous investigation is warranted in order to adequately evaluate the safety, efficacy, and long-term oncologic and functional benefits of robotic rectal cancer surgery.

Complications of Surgical Therapy for Rectal Cancer

Complications of surgical therapy for rectal cancer include all of the complications associated with major abdominal surgery (e.g., bleeding, infection, ureteral or adjacent organ injury, and bowel obstruction), with the addition of some complications that are unique to pelvic surgery. Specifically, anastomotic leak occurs in 5% to 15% of cases overall, with increased rates in association with lower anastomoses, immunocompromised states, and preoperative radiation. A defunctioning stoma will decrease the morbidity of such a leak and may decrease the leak incidence. At MDACC, a diverting loop ileostomy is typically constructed for all patients who have received preoperative radiation. Additional factors which, if present, should make the surgeon strongly consider a diverting ileostomy include: anastomosis within 7 cm of the anal verge, CAA, or suboptimal tissue quality. Autonomic nerve preservation is always performed during pelvic dissections, unless tumor involvement necessitates the sacrifice of these structures. With careful dissection during TME, 75% to 85% of patients have a return to preoperative sexual and urinary function. Other complications include urinary dysfunction, stoma dysfunction, perineal wound complications, hemorrhage from presacral vessels, and anastomotic stricture. The mortality rate from surgical resection varies from less than 2% to 6%.

Adjuvant Therapy of Rectal Cancer

Currently, the NCCN guidelines recommend adjuvant chemotherapy for all stage II and III rectal cancers patients. The recommended duration of therapy is 6 months. However, strong evidence for use of adjuvant chemotherapy after neoadjuvant chemoradiation is lacking. In the

CAO/ARO/AIO-04 trial, adjuvant chemotherapy was administered to nearly all (89%) patients who received preoperative chemoradiation but only 50% of the patients who received postoperative chemoradiation. Despite these significantly different rates of adjuvant chemotherapy administration, there was no difference in OS or in distant recurrence rates, thus raising the question of benefit from adjuvant chemotherapy. The EORTC Radiotherapy Group Trial 22921 had a 2×2 trial design and investigated the addition of 5-FU adjuvant chemotherapy to preoperative radiation or preoperative chemoradiation in stage II/III rectal cancer. The addition of adjuvant 5-FU was not associated with any difference in local recurrence, distant metastases, or OS rates. In the ADORE trial from Korea, 321 patients with pathologic stage II or III rectal cancer after having undergone neoadjuvant long-course chemoradiation and standard resection, were randomized to receive adjuvant 5-FU and leucovorin or adjuvant FOLFOX. After subgroup analyses, patients with residual pathologic stage III rectal cancer demonstrated superior DFS at 3 years with adjuvant FOLFOX when compared to adjuvant 5-FU. Of particular interest is the question of adjuvant therapy in patients undergoing neoadjuvant chemoradiation followed by surgical resection with a complete pathologic response (ypT0N0). Current NCCN guidelines recommend adjuvant systemic treatment in this setting. The data supporting this is inconclusive as meta-analyses of randomized trials in this patient population have demonstrated divergent conclusion.

Intraoperative Radiation Therapy

IORT can be used for both recurrent and locally invasive rectal cancer. Its advantages include increased local control in high-risk cancers, accurate treatment of focal areas at risk, and the ability to shield sensitive structures. Even in the setting of adequate preoperative chemoradiation, high-risk tumors will still have a high local recurrence rate in large part due to locoregional extension. IORT allows treatment of areas with close or microscopically positive margins in this situation. Dosing depends on the clinical situation and the total preoperative radiotherapy dose: 12 to 13 Gy is given for close margins (<3 mm), 15 Gy is given for microscopically positive margins, and 17 to 20 Gy is used for areas of gross residual disease. An alternative approach is intraoperative brachytherapy. This allows radiation access in areas where the IORT beam cannot be focused due to anatomical constraints of the pelvis. At MDACC, intraoperative

brachytherapy (10 to 20 Gy) is used selectively in patients with locally advanced or recurrent disease where there is a close or microscopically positive margin as demonstrated by frozen section.

M. D. Anderson Experience

Our preferred treatment strategy of clinically T3 or N+ locally advanced rectal cancer is neoadjuvant long-course radiation with concurrent 5-FU or capecitabine. We deliver 45 Gy of preoperative radiation therapy in 25 fractions with a boost to the tumor bed of 5.4 Gy in 3 fractions for a total of 50.4 Gy in 28 fractions. This is followed by surgery and then adjuvant chemotherapy. For clinically T4 or N2 disease we will consider starting with induction chemotherapy typically with FOLFOX for 4 cycles, followed by concurrent chemoradiation, followed by surgery. This strategy treats micrometastatic disease early, allows for downsizing bulky primary disease, and adds to the degree of pathologic response derived from chemoradiation alone. This approach also allows us to test tumor biology in a patient population that is at high risk for the development of distant disease. Most patients receive adjuvant chemotherapy. Watchful waiting has emerged as a novel treatment option among patients who achieve a complete clinical response to neoadjuvant chemoradiation. However, selection of the optimal patients for this approach has remained elusive and close surveillance is needed if patient and surgeon elect to choose this option.

SURVEILLANCE

Patients with a history of colorectal carcinoma require close surveillance. However, data to demonstrate a survival advantage from an intensive surveillance program has been limited. In a Danish prospective study, 597 CRC patients were randomized to either close follow-up (every 6 months for the first 3 years) or routine follow-up (every year) for 3 years, using examination, stool heme test, colonoscopy, laboratory testing, and chest radiograph. The frequency of recurrent cancer was the same in both groups, but it was diagnosed earlier in the close follow-up group. The close follow-up group had more resections for curative intent (local and distant), but cancer-specific survival (CSS) differences have been more difficult to demonstrate. Table 12.4 outlines current endoscopic guidelines for CRC patients. In general, close follow-up including regularly

scheduled CEA level determination during the first 2 years followed by less intensive follow-up during years 3 to 5 are advocated.

At MDACC, the surveillance intensity and frequency are tailored to individual patients, and key factors considered including: disease stage, comorbidities, eligibility for salvage treatment, and the priorities and preferences of the patient. In general, history, physical examination, and laboratory tests including CEA are performed every 3 to 4 months for the first 2 to 3 years after surgery, and every 6 months during years 3 or 4 through 5, and yearly thereafter for a total of 5 to 8 years. Colonoscopy is performed after 1 year if the proximal colon had been examined preoperatively or after 6 months if the proximal colon had not been examined preoperatively. If normal, it is then repeated after an interval of 3 years, with a life-long interval of every 3 to 5 years. CT scans of the chest abdomen and pelvis are also obtained every 3 to 6 months for 2 to 3 years and every 6 to 12 months for up to 5 years.

RECURRENT AND METASTATIC DISEASE

Among the patients who develop recurrences, 85% do so during the first 2.5 years after surgery. The remaining 15% experience recurrence during the subsequent years. Recurrence develops in less than 5% of patients who are disease-free at 5 years. The risk of recurrence is higher with higher-stage disease. Other recurrence risk modifiers include race, grade of tumor, aneuploidy, as well as environmental factors such as smoking and obesity. Recurrences may be local, regional, or distant. Distant recurrence, the most common presentation, occurs either alone or concomitantly with locoregional recurrence. Local recurrence can develop in up to 15% of the patients undergoing initial curative intent resection for rectal cancer and the risk is increased with non-R0 resections. When local recurrence is isolated, complete salvage resection with R0 margins in combination with multimodality therapy can result in a 5-year survival rate of up to 54% after salvage. Recurrence isolated to the anastomosis (intramural) is rare but is typically technically easier to salvage than recurrences that involve the lateral pelvis.

The most common sites of distant metastases from rectal cancer are the lung and liver depending on the distance of the tumor to the anal verge. Retroperitoneal nodal disease and peritoneum are two additional patterns of distant failure. Recurrences can present with a constellation of symptoms ranging from the vague and nonspecific to the clinically overt.

Serum CEA level provides added insight in postoperative monitoring. It is most useful in patients in whom levels were increased preoperatively and returned to normal following surgery. Levels should be determined preoperatively, 6 weeks postoperatively, and then according to the schedule described in the surveillance section. The absolute level and rate of increase in CEA and the patient's clinical status are important factors to consider. Postoperative CEA levels that do not normalize within 4 to 6 weeks suggest incomplete resection or recurrent disease, although false-positive results do occur. CEA levels that normalize postoperatively and then start to increase are suggestive of recurrence. This may represent occult or clinically obvious disease. A rapidly increasing CEA level may more likely suggest liver or lung involvement, whereas a slow, gradual rise is more likely to be associated with locoregional disease. Despite the reliability of an increased CEA level in predicting tumor recurrence, 20% to 30% of patients with locoregionally recurrent tumors have a normal CEA level. Poorly differentiated tumors may not make CEA, which is one explanation for such false-negative results. In contrast, CEA is increased in 80% to 90% of patients with hepatic recurrences. A prospective randomized trial evaluated the significance of CEA in follow-up in 311 asymptomatic patients. Patients with increased CEA levels were followed until symptoms developed; then a full workup was initiated. The sensitivity, specificity, and positive predictive values of an increased CEA level were 58%, 93%, and 79%, respectively. The median lead-time of the increased CEA to detection by other means was 6 months. Seven percent of patients who had an increased CEA failed to have identifiable recurrent disease on workup. Two meta-analyses have been performed pooling results from five randomized studies and a survival advantage in patients allocated to intensive follow-up with CEA has been shown. The German CRC Study Group evaluated follow-up CEA levels in 1,321 patients after curative resection and determined that CEA monitoring was beneficial in 47% of patients with recurrence and 11% of patients overall; however, only 2.3% underwent a curative R0 resection of recurrent disease. Results from a UK multicenter randomized prospective trial of protracted infusion 5-FU versus bolus 5-FU in the adjuvant setting demonstrated that both CT and CEA were valuable components for postoperative follow-up and resulted in improved survival. Despite significant interest, the use of radiolabeled monoclonal antibodies (mAb) directed against tumor-specific antigens and CEA have not been shown to be useful for imaging the extent

and location of metastases.

PET scan with 2-(^{18}F)fluorodeoxy-D-glucose (FDG) has been reported to have 89% positive predictive value and excellent negative predictive value in patients who had a rising CEA and normal conventional radiography. FDG–PET imaging relies on the increased metabolic uptake of glucose (fluorine-labeled analog of 2-deoxyglucose or FDG) in tumors compared with normal tissues and sometimes may help to distinguish postradiation fibrosis from recurrent tumor.

In the era prior to modern imaging technology, if the metastatic evaluation was negative in the face of increased CEA level, a second-look laparotomy would be indicated. Studies from that time period have reported that approximately 60% to 90% of patients with asymptomatically increased CEA levels were found to have recurrent disease at laparotomy; 12% to 60% of whom had resectable disease.

Treatment of the asymptomatic patient with an increased CEA level can be challenging. An increased level should be confirmed by a repeat CEA determination. A thorough clinical investigation should include LFTs, CT scan of the chest, abdomen, pelvis, and colonoscopy. At MDACC, we routinely monitor CEA values because of the potential to detect site of disease relapse that may be amenable for salvage therapy, especially within the liver. This allows for the potential identification of a subgroup of patients who may benefit from salvage intervention. PET scans are not routinely performed for surveillance, but only utilized to evaluate patients with rising CEA values where conventional cross-sectional imaging does not identify the site of recurrence. Early detection of asymptomatic disease results in a higher resectability rate than when resection is attempted for symptomatic disease (60% vs. 27%). The liver is the most common site of recurrence, followed by adjacent organs, the anastomotic site, and the mesentery. Resectability rates correspond to the level of CEA elevation, with CEA levels less than 11 ng/mL being associated with higher resectability rates.

Treatment of Recurrent Locoregional CRC

The appropriate treatment of resectable recurrent disease depends on the location of the disease. Potentially resectable recurrent disease is treated in a multimodality fashion using preoperative chemotherapy (with or without radiation or re-irradiation), surgery, and IORT (if available). For recurrence involving the sacrum, en bloc sacral resection can sometimes

result in 4-year survival rates of 30%. Contraindications to sacral resection include pelvic sidewall involvement, sciatic notch or ala involvement, bilateral S2 involvement, encasement of common or external iliac vessels, and extra pelvic disease. Given the extent of surgery required and the high rates of morbidity associated with salvage resections, resection for the sole purpose of palliation should be carefully deliberated and alternative procedures that may alleviate symptoms without the high risk for complications should be considered first. At MDACC, patients presenting with locally recurrent rectal cancer are evaluated by CT chest, abdomen, pelvis, MRI pelvis, and PET/CT. Potentially resectable pelvic recurrences are evaluated for candidacy for re-irradiation. Those who are candidates typically undergo preoperative chemotherapy and re-irradiation, while others are considered for preoperative systemic chemotherapy. Every effort is made to achieve an R0 resection, and IORT is utilized for close or R1 resection margins. Using this approach in 229 patients with locally recurrent and re-recurrent rectal cancer, multimodality salvage therapy resulted in a 5-year OS of 50%. Although the usual surgical procedure for resectable recurrent rectal cancer is salvage APR or pelvic exenteration, very select cases can be treated with sphincter preservation.

Surgical Treatment of Metachronous Liver Metastasis

The liver is the most common site of visceral metastases, and it is the only site affected in up to 20% of patients with recurrent CRC. Recent data from MDACC demonstrates that surgical resection of hepatic metastases now offers the potential for 5-year survival up to 58%. Colorectal hepatic metastases are discussed in detail in Chapter 12.

Lung

Pulmonary metastases occur in 10% to 20% of patients with CRC. They are typically found in association with concurrent hepatic metastases. Isolated pulmonary metastases occur most commonly with distal rectal lesions because the venous drainage of the distal rectum bypasses the portal system and allows metastasis to travel directly to the lungs.

The finding of a solitary lesion on a chest radiograph should prompt evaluation with thoracic CT scanning and, for a centrally located lesion, bronchoscopy with biopsy. Peripheral lesions may be amenable to CT-guided needle biopsy or video-assisted thoracoscopic surgery. Fifty

percent of patients with solitary pulmonary nodules will have primary lung tumors rather than colorectal metastases.

Patients with locally controlled primary tumors, no evidence of metastases elsewhere, good pulmonary reserve, and low medical risk are candidates for resection. Patients with solitary metastases experience the best survival, but patients with as many as three lesions (unilateral or bilateral) can experience up to a 40% 5-year survival. As in liver resection for metastatic disease, the optimum surgery includes achievement of negative margins at resection without the routine use of pneumonectomy.

The overall 5-year survival rate following resection of pulmonary metastases can approach 40%. Age, gender, location of the primary disease, disease-free interval, or involvement of hilar or mediastinal lymph nodes does not seem to influence survival. The number of metastases in most series is inversely correlated with 5-year survival. Recurrence confined to the lung after resection is an indication in select patients, for repeat resection.

Bone and Brain

Metastatic disease to the brain is uncommon and usually occurs after established lung involvement. Symptomatic solitary lesions can be treated by palliative craniotomy and resection. In a very small subpopulation of patients, cranial disease may be the only site of involvement, and excision in this setting may increase survival. Bone metastases are uncommon but are best managed with radiation therapy especially when symptomatic.

Ovary

Because 1% to 8% of women who undergo potentially curative CRC resections subsequently develop ovarian metastases, prophylactic oophorectomy at the time of colectomy has been considered for postmenopausal patients. However, prophylactic oophorectomy has not been shown to improve survival and therefore is not routinely performed, but grossly abnormal ovaries should be removed. When isolated metastatic disease to the one ovary is identified, bilateral oophorectomy is the procedure of choice even if the contralateral ovary appears grossly normal, because there is a high risk for bilateral involvement.

TARGETED THERAPIES FOR CRC

Dramatic improvements have been seen in overall and DFS for CRC with the introduction of cytotoxic chemotherapy agents such as fluorouracil, oxaliplatin, and irinotecan. However, not all patients and their tumors respond to these drugs, leaving some individuals to suffer the severe side effects of these therapies without significant benefit. Precision medicine aims to shift treatment regimens from a population approach based on TNM staging to a personalized approach based on a patient's unique tumor characteristics. Recent advances in molecular biology and epigenetics have identified several biomarkers of prognostic and predictive significance in CRC that will be briefly described below.

Vascular Endothelial Growth Factor

VEGF signaling via the VEGFR2 receptor is a potent regulator of angiogenesis. Signaling results in endothelial cell proliferation and migration. Consequently, VEGF overexpression has been associated with worse outcomes related to tumor progression and poor OS in patients with CRC. Bevacizumab was the first anti-angiogenic targeted drug to be FDA approved for the treatment of metastatic CRC. The drug is a recombinant monoclonal antibody against VEGF-A. When added to traditional cytotoxic chemotherapy bevacizumab results in an increased response rate in metastatic CRC patients and leads to longer progression-free survival (PFS) and OS. Additionally, bevacizumab in combination with FOLFOX (5-FU, oxaliplatin, leucovorin)/FOLFIRI (5-FU, leucovorin, irinotecan) has been found to enhance response in patients with potentially resectable metastases and had increased the number of patients able to undergo curative-intent hepatic metastasectomy. Of note, the drug is associated with impaired wound healing and should be discontinued at least 4 weeks prior to elective surgery.

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) signaling activates the Ras/Raf/MAPK and the phosphatidylinositol 3-kinase (*PI3K)* signaling pathways leading to cellular proliferation, inhibiting apoptosis and promoting cellular invasion. EGFR activation likely not only contributes to CRC tumorigenesis, but also to CRC metastasis. Two classes of anti-EGFR therapies were developed to target this mechanism; tyrosine kinase inhibitors (TKIs) and monoclonal antibodies to EGFR. TKIs, such as

gefitinib and erlotnib, block EGFR activity and preferentially suppress PI3K signaling in CRC but are associated with severe GI toxicity and are poorly tolerated. Cetuximab was the first EGFR monoclonal antibody (mAb) to be FDA-approved for the treatment of metastatic CRC. The drug binds to EGFR and inhibits both MAPK and PI3K cell signaling. Cunningham et al. reported improved PFS and OS with single agent cetuximab or when used in conjunction with irinotecan in mCRC patients with refractory disease. Panitumumab, another EGFR mAb, showed a similar response and was FDA approved soon after.

KRAS/NRAS

The RAS family of proteins (KRAS, NRAS, and HRAS) act downstream of EGFR-mediated cellular signaling (Fig. 12.5). KRAS mutations occur in 30% to 40% of CRCs, while NRAS mutations are rare at 5% and HRAS is not seen in CRC. In retrospective analysis of several clinical trials of anti-EGFR mAbs, wild type–KRAS was found to be required for anti-EGFR antibody-mediated response. Because these proteins act downstream of EGFR, KRAS/NRAS mutations result in constitutive activation of the Ras-Raf-MAPK pathway and confers tumor resistance to anti-EGFR therapies. Current guidelines require testing for KRAS and NRAS prior to initiating anti-EGFR therapy. KRAS mutations appear to also confer poor prognosis in metastatic CRC.

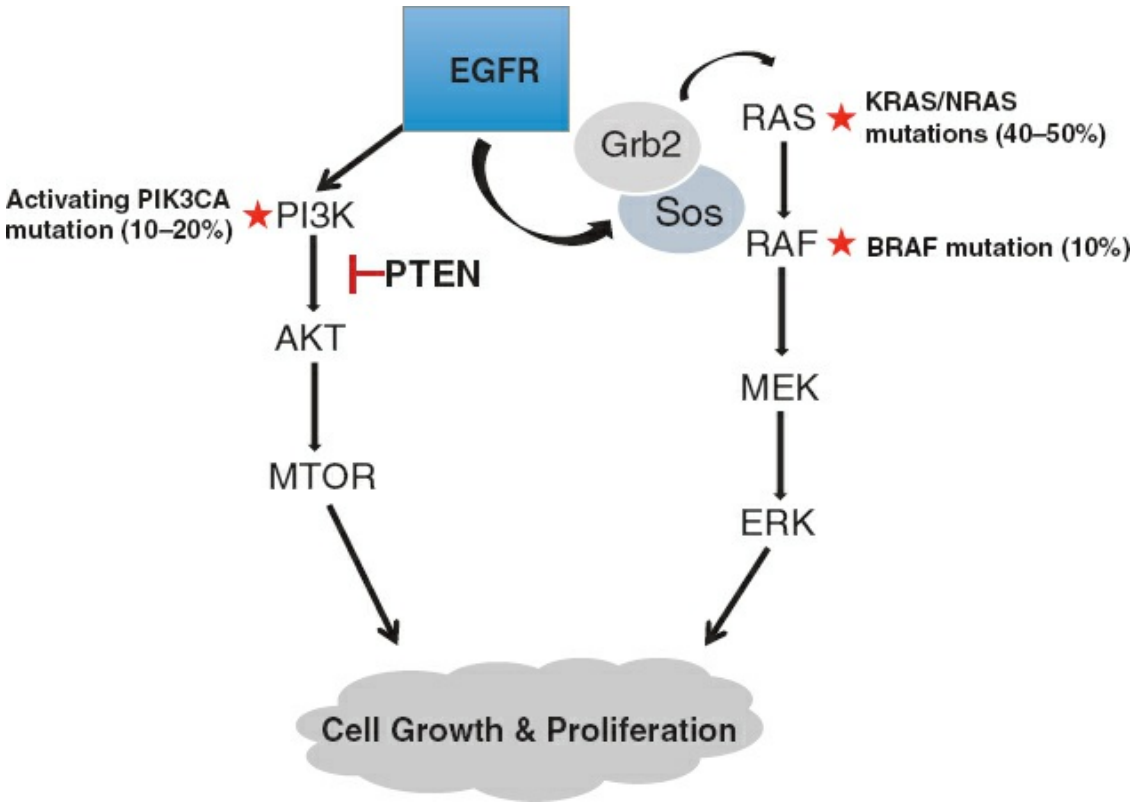

Figure 12.5 EGFR signaling pathway.

BRAF

The BRAF oncogene is another modulator of the MAPK pathway downstream from RAS. BRAF mutations result in the development of CRC via the serrated pathway. BRAF mutant tumors are more prevalent in women and older patients (>70 years). These tumors are usually right-sided, MSI-high, mucinous, and poorly differentiated. BRAF mutant CRCs exhibit a unique pattern of metastatic spread, often bypassing the liver and developing lung or peritoneal disease. BRAF-mutated metastatic CRC is associated with poorer OS likely because metastatic disease sites are not amenable to resection. BRAF mutations also contribute to cetuximab resistance, though perhaps not as potently as KRAS. Studies are ongoing to investigate the role of targeted BRAF therapy in CRC using drugs previously approved for treatment in melanoma.

Human Epidermal Growth Factor 2 (HER2) Gene Status

HER2 gene amplification and protein overexpression occurs in 5% to 12% of colon cancer and as high as 26% of rectal cancers. Its prognostic and predictive relevance in CRC is currently being investigated. One study

demonstrated improved CSS in patients with advanced HER2-positive rectal cancers while others have shown HER2-amplified CRC do worse. The recent HERCULES trial investigated the effect of dual anti-HER2 therapy in mCRC. In this small phase 2 study, after a median follow-up of 94 weeks, 8 patients (30%) responded to therapy, 1 patient (4%) had a complete response, and 12 patients (44%) had stable disease suggesting a novel therapeutic target for CRC albeit in only a small percentage of patients.

Mismatch Repair and Tumor Immunity

Until recently, tumor immunity was not considered a major driver of CRC. However, recent studies have demonstrated that CRC that display high lymphocyte infiltration in particular cytotoxic/T helper 1 lymphocytes (CTL/Th1) are associated with improved PFS and OS. MSI-high tumors are especially immune driven with significant lymphocyte infiltration and overexpressed PD1 and PD-L1 immune checkpoints. Pembrolizumab, a monoclonal antibody against PD-L1 and PD-L2, has demonstrated promising responses in patients with advanced CRC and is being further investigated. These responses were seen in MSI-H tumors suggesting that MMR status is likely a predictive biomarker for checkpoint inhibition.

UNCOMMON COLORECTAL TUMORS

Lymphoma

Lymphoma is uncommon in the colon/rectum occurring in 0.4% of patients; intestinal lymphoma and can present anywhere between the second and eighth decades of life. Almost all are non-Hodgkin lymphomas. Twenty-five percent of patients may present with fever, occult blood loss, anemia, a palpable mass, or an acute abdomen. A history of abdominal pain, fever, and weight loss in a patient who is younger than the expected age for a colorectal tumor should raise the suspicion of intestinal lymphoma.

Abdominal CT and endoscopy with biopsy are the most useful diagnostic tests. A thickened bowel segment, adjacent organ extension, or nodal enlargement may be seen. If the lesion is intraluminal, endoscopic biopsy will facilitate the diagnosis. Most of these lesions are intermediate- to high-grade B-cell lymphomas. If a diagnosis is made preoperatively in

an otherwise asymptomatic patient, bone marrow biopsy should be performed. A primary lesion is defined as a lesion with no associated organ or lymphatic involvement, negative chest CT, and a negative peripheral blood smear and bone marrow.

Surgery is performed in the clinical setting of obstruction, bleeding, perforation, or an uncertain diagnosis. In rare cases, surgery may be performed for complete resection of a primary lesion. A thorough exploration is performed, and all suspicious nodes or organs are biopsied to assess the stage of disease. The primary intestinal lesion should be resected with negative margins whenever possible. The bowel mesentery should be resected with the tumor so regional nodes can be assessed pathologically. Intestinal continuity should be restored whenever possible. If a large tumor is found to be unresectable and is obstructing the bowel, a bypass can be performed. Surgical clips should be placed to facilitate identification of the tumor by the radiation oncologist.

Intestinal lymphoma is mainly treated by chemotherapy, with or without radiation, and surgery is performed to avoid complications. For rectal lymphoma, complete resection is followed by radiation treatments to the pelvis. Chemoradiation is used if the resection was incomplete. The OS for stage I and II diseases is approximately 80%. This decreases to 35% with advanced disease.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) account for most mesenchymal tumors arising in the wall of the colon or rectum. Primary colorectal GISTs are rare and comprise less than 1% of colonic tumors. GISTs have recently been characterized and historically classified as: leiomyomas, leiomyosarcomas, neurofibromas, and schwannomas and are further discussed in Chapter 5. In a review of 1,458 cases of malignant GISTs from 1992 to 2000 in the SEER database, 7% were located in the colon and 5% in the rectum. These tumors can present as small submucosal or as large intramural masses. Patients can present with pain, bleeding, obstruction, nausea, vomiting, anemia, tenesmus, or hematuria. Ulceration may be present in 30% to 50% of patients. A thorough clinical evaluation should be conducted to exclude metastatic disease. Excision with negative surgical margins is the treatment of choice. Colonic tumors are excised with adjacent mesentery. Extended nodal excision is not indicated in the absence of clinically evident disease. Small tumors of the rectum and anal

canal can be removed transrectally or endoscopically. Criteria similar to GISTs elsewhere in the GI tract, are used for determining the need for adjuvant therapy with imatinib mesylate (STI-571, Gleevec), a monoclonal antibody to the tyrosine kinase receptor.

Neuroendocrine Tumors

Neuroendocrine tumors classified as low grade (carcinoid) or high grade are uncommonly found in the colon and rectum. Approximately 18% to 30% of intestinal carcinoids occur in the rectum or rectosigmoid, 4% to 15% occur in the colon, and 4% to 50% have been reported to occur in the appendix. They are usually discovered incidentally unless they are large. After histologic grade, size and depth of invasion are the best predictors of clinical behavior. Hindgut carcinoids are almost never biochemically active and therefore do not cause carcinoid syndrome. Although large tumors may present with bleeding, obstruction, or constipation, tumors less than 2 cm are frequently asymptomatic. Diagnosis is made by endoscopic biopsy. In general, tumors less than 1 cm rarely metastasize, whereas those greater than 2 cm have increased metastatic potential; in the 1- to 2-cm range, 10% to 20% will metastasize. This makes treatment decisions for tumors in the 1- to 2-cm range problematic. Small lesions (<1 cm) are commonly well differentiated and can be adequately treated with endoscopic excision. Lesions less than 2 cm can be treated with full-thickness local excision. High-grade tumors have a poorer overall prognosis, and the role of radical resection as well as of any neoadjuvant chemo/chemoradiation therapy must be deliberated in a coordinated and multidisciplinary fashion.

ANAL CANCER

Epidemiology and Etiology

Approximately 5,000 new cases and 700 deaths from anal cancer occur annually in the United States. Although anal carcinoma has been considered an uncommon cancer, the incidence in the United States has increased by approximately 1.6-fold for men and 1.5-fold for women from the time period 1973–1979 to 1994–2000. In the HIV-infected population, the standardized incidence rate of anal carcinoma had been estimated to be 19/100,000 in the time period 1992–1995, but dramatically increased to

78.2/100,000 during the time period 2000–2003. Other causes of immunocompromise such as transplantation or immunotherapy for autoimmune diseases are additional risk factors. Kidney transplant patients have at least a fourfold increased incidence of the disease. In the general population, elderly women and men in their 60s are at the highest risk for anal cancer, with women having the greater risk.

Population-based evidence has established that anal cancer is a sexually transmitted disease (STD) in much the same way that cervical cancer is an STD. Women with anal cancer are more likely to have had a history of genital warts or other STDs and men with anal cancer are more likely to have reported homosexual activity or to have had a history of genital warts or gonorrhea. As with cervical cancer, anal cancer has been linked to human papillomavirus (especially HPV-16 and HPV-18) infection. Studies have shown that 40% to 95% of anal cancers harbor HPV DNA, with the strongest association seen with nonkeratinizing squamous cell types originating from the squamous mucosa of the anal canal. This association has proven to be even stronger with advances in HPV detection techniques showing the presence of HPV-16 and HPV-18 in up to 88% of patients with anal carcinoma.

The national cancer registries in Denmark and Sweden identified 417 patients with anal cancer between 1991 and 1994 and compared them with 534 controls with rectal adenocarcinoma and 554 population controls. Using multivariate analysis while adjusting for smoking and education, this study found that in women, the lifetime number of sexual partners especially those with STDs, a history of anal intercourse, a history of anogenital warts, gonorrhea, or cervical neoplasia, and testing for HIV were associated with a significantly increased risk for anal cancer. Risk factors for men included lifetime number of sexual partners, homosexuality, history of anal warts or syphilis, and being unmarried with or without a current sexual partner. The associations were similar when data from Denmark and Sweden were considered separately or together. When polymerase chain reaction for HPV DNA was performed on archived tissue specimens from these patients, 88% of patients overall were positive for HPV, with 83% HPV-16 positive. In comparison, HPV-16 is responsible for about 50% of cervical cancer cases, and additional HPV types such as HPV 18, 31, and 45 are responsible for an additional 30%. Analysis of the data from the SEER program revealed that the relative risks of anal cancer in women who had been diagnosed with

invasive cervical cancer was 4.6 when compared to general population. This increased risk for anal cancer in women with cervical dysplasia or cancer, and their sexual partners, is likely through autoinoculation by the virus that caused the cervical dysplasia.

Anal cancers can be located within the anal canal or in the perianal skin (anal margin). Anal canal cancers are three to four times more common in women than in men. Anal margin cancers (tumors of the hair-bearing perianal skin) are more common in males. There are significantly more cases of anal margin cancers in homosexual males.

Pathologic Characteristics

More than 60% of malignant anal lesions are histologically SCCs. With the exception of melanoma, small cell carcinoma, and anal adenocarcinoma, all other histologic subtypes behave similarly and are treated according to their anatomical location. Basaloid carcinoma (basal cell carcinoma with a massive squamous component), mucoepidermoid carcinoma (originating in anal crypt glands), and cloacogenic carcinoma are all variants of squamous carcinoma. As with cervical cancer, SCC of the anus may be preceded by or coexist with premalignant dysplasia or anal intraepithelial neoplasia (AIN).

The prognosis of anal margin cancers is favorable. The rate of local recurrence is higher than the rate of distant metastases, which are rare. When they do occur, metastases are most commonly found in the superficial inguinal lymph nodes (approximately 15% of cases). It is unusual for anal margin cancers to metastasize to mesenteric or internal iliac nodes.

Anal canal cancers are associated with aggressive local growth and if untreated will extend to the rectal mucosa and submucosa, subcutaneous perianal tissue and perianal skin, ischiorectal fat, local skeletal muscle, perineum, genitalia, lower urinary system, and the broad ligament. Historically, mesenteric lymph node metastases have been detected in 30% to 50% of surgical specimens. More than 50% of patients will present with locally advanced disease. The most common sites of distant metastases are the liver, lung, and abdominal cavity. However, most cancer-related morbidities are due to uncontrolled pelvic or perineal disease.

Diagnosis

The initial symptoms of anal cancer include bleeding, pain, local fullness, and other symptoms consistent with a malignant fistula. The more common benign anal diseases, which accompany anal cancer in more than 50% of cases, can present with similar symptoms. A detailed history, including previous anal pathology and sexual habits, should precede a meticulous physical examination. Physical examination should attempt to identify the lesion, its size and anatomical boundaries, and any associated scarring or condylomata. It is also important to determine the resting and voluntary anal sphincter tone. Occasionally, an examination under general anesthesia may be necessary to complete the local evaluation. Cross-sectional imaging of the chest, abdomen and pelvis is important in assessing extent of local disease and distant spread. Proctosigmoidoscopy is essential to assess the proximal extent of disease and to obtain tissue for biopsy. Palpable inguinal lymph nodes should be evaluated by fine-needle aspiration. PET–CT may be helpful in the workup for lesions in the anal canal to evaluate for distant metastases.

TABLE 12.9 American Joint Committee on Cancer Staging of Anal Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor no larger than 2 cm
T2	Tumor >2 cm but <5 cm
T3	Tumor > 5 cm
T4	Tumor invading other organs (urethra, bladder, vagina, etc.)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac lymph nodes with any N1a nodes
Distant Metastases (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases present

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIIA	T1–T3	N1	M0
IIB	T3	N0	M0
IIIB	T4	N0	M0
IIIC	T3–T4	N1	M0
IV	Any T	Any N	M1

Staging

The current AJCC staging system for anal margin and anal canal cancers is depicted in Table 12.9.

Treatment

Anal Canal

Until the 1980s, APR with permanent colostomy was the recommended treatment for all SCCs of the anal canal. This treatment, however, was associated with low survival rates as a result of distant failure. Radiation therapy in the range of 50 to 60 Gy was also used as definitive treatment of these cancers, with recurrence and survival rates similar to those seen

using APR. The pioneering chemoradiation protocol developed by Nigro et al. (1974), which has since been confirmed and modified by others, has radically changed the approach to this disease.

Currently, well-differentiated anal margin lesions characterized as T1N0 are treated with wide local excision to grossly negative margins. For anal canal tumors, surgical intervention is reserved for the following indications: (a) APR for salvage treatment in patients with persistent disease (within 6 months of chemoradiation) or recurrent disease (after 6 months); (b) APR or exenterative procedures for severely symptomatic patients (perineal sepsis, intractable urinary or fecal fistulae, and intolerable incontinence); (c) inguinal lymph node dissection for persistent inguinal disease, recurrent inguinal disease (treated first with radiation therapy unless associated with local recurrence), or for bulky or fungating or symptomatic primary disease in the inguinal basin; and (d) palliative fecal diversion in patients with obstructing, fistulizing, nearly obstructing lesions.

Since the initial work of Nigro et al. (1974), studies have been performed to dissect out the vital components and doses of the chemoradiation in order to optimize treatment. There is evidence that (a) higher doses of radiation produce better local control rates using a constant mitomycin-C dose (Rich, 1997); (b) 5-FU and mitomycin-C with radiation therapy produces better local control rates than radiation therapy alone; (c) 5-FU and mitomycin-C with radiation therapy produces better local control rates than 5-FU alone with radiation therapy; and (d) 5-FU and cisplatin with radiation therapy produces local control and survival rates similar to 5-FU, mitomycin-C, and radiation therapy with less toxicity. The randomized intergroup RTOG 98-11 trial investigated the use of mitomycin or cisplatin with 5-FU-based chemoradiation therapy in patients with SCC of the anus. Patients were randomly assigned to receive either concurrent chemoradiation therapy with 5-FU/mitomycin or induction chemotherapy with 5-FU and cisplatin for two cycles followed by concurrent chemoradiation therapy with 5-FU/cisplatin. No significant differences were seen in 5-year overall or DFS. Moreover, the colostomy rate was significantly increased in the cisplatin-containing arm. However, the mitomycin arm of this study was compared the cisplatin arm which included both induction chemotherapy and chemoradiation. Therefore, the trial has been criticized with respect to its generalizability to all cisplatin-based strategies. The phase III UK ACT II trial was designed to compare

5-FU/mitomycin to 5-FU/cisplatin with concurrent radiation of 50.4 Gy with or without additional systemic chemotherapy. No significant difference was observed in 5-year colostomy-free survival rates among any of the four arms. Additionally these investigators showed that the optimal time for assessing clinical response to chemoradiation was 26 weeks after its initiation.

The current regimen for primary treatment of SCC of the anal canal is chemoradiation therapy (Table 12.10). At MDACC we utilize a 5-FU and cisplatin-based chemoradiation protocol because of decreased toxicity and similar response, survival, and colostomy data. Complete responses with this treatment can be expected in up to 90% of patients, with 5-year survival rates approaching 85%.

TABLE 12.10 Current and Classic Treatment Protocols for Anal Canal Cancer

Current	External-beam radiation therapy 5 d/wk for total dose of 45–55 Gy
	5-FU, 250 mg/m^2/day, M–F for the entire duration of radiation
	Cisplatin, 4 g/m^2/day, M–F for the entire duration of radiation
Classic	5-FU, 750–1,000 mg/m^2 over 24-hour continuous IV infusion
Days 1–4	Mitomycin C, 10–15 mg/m^2, IV bolus
Day 1	Radiation therapy 5 d/wk for total dose of 45–55 Gy; boosts of up to 60 Gy
Days 1–35	may be given to the anus and/or inguinal basins5-FU, 5-fluorouracil; IV,
Days 29–32	intravenous
	5-FU, 750–1,000 mg/m^2 over 24-hour continuous IV infusion

5-FU, 5-fluorouracil; IV, intravenous.

The presence of a persistent mass on examination 12 to 14 weeks after chemoradiation is an indication for biopsy because a persistent mass after therapy will demonstrate cancer on biopsy in 18% to 34% of cases. The timing of the assessment for determining whether there is persistent disease is critical. There are reports of positive biopsy results taken at 6 to 8 weeks after therapy (persistent disease) reverting to negative biopsy results when taken later in patients who refused surgery. This implies that there may be a delayed radiation effect for up to several months after treatment. At MDACC, we do not routinely obtain a biopsy specimen of the treated tumor site unless gross abnormalities are present; the first assessment occurs at approximately 8 weeks after completing chemoradiation but up to 24 weeks is given before operating on persistent

disease.

Patients with persistent or locally recurrent disease are typically salvaged with APR with or without adjacent organ resection, with a resultant 50% 5-year survival. Additionally, cisplatin-based chemotherapy with re-irradiation therapy has been used successfully to salvage up to one-third of patients with recurrent disease.

Anal Margin

SCC of the anal margin is defined currently by the AJCC as a lesion originating in an area between the anal margin and 5 cm in any direction onto the perianal skin and is classified with skin tumors. The terms anal margin and perianal skin are often used synonymously. Note that the data supporting the treatment of these uncommon, heterogeneous lesions derive from small, single-institution, mostly retrospective studies. Moreover, many of these studies include lesions of the lower anal canal (dentate to anal verge) that were included previously in older definitions of the anal margin. The rationale for any modality of therapy derives from the proportional increase in chance of metastases with increasing tumor size; in tumors less than 2 cm, lymph node metastases are rarely found. For lesions between 2 and 5 cm, and those greater than 5 cm, the rates are 24% and 25% to 67%, respectively.

Small (<2 cm), superficial T1, well-differentiated anal margin cancers that do not invade the sphincter complex can be treated by a negative-margin wide local excision alone, with a 5-year survival rate greater than 80%. Wide local excision may include parts of the superficial internal and external anal sphincters without compromising anal continence. Positive margins can be re-excised or consideration given to radiation therapy with or without 5-FU–based chemotherapy.

Larger T2 to T4 or N-positive lesions are best treated with multimodality therapy using chemoradiation, as in anal canal cancers, given the higher local recurrence rate. Inclusion of bilateral inguinal/low pelvic nodal regions in the radiation field should be considered. Lymph node dissection is reserved for those patients with residual or recurrent disease. It is not known whether the treatment of inguinal disease translates into improved survival. Patients with T3 to T4 and poor sphincter function may require APR. For all patients, the 5-year disease-specific survival is 71% to 88%, and the local control rate after initial therapy is 70% to 100%. Platinum-based chemotherapy is recommended

for metastatic disease.

Surveillance

Patients should be followed for detection of local and systemic failures and treatment complications. Local inspection, digital examination, and anoscopy are recommended between 8 and 12 weeks after chemoradiation treatment and every 3 to 6 months for 2 to 3 years and then yearly thereafter. A biopsy is performed only if gross disease is suspected after serial digital examinations. Biopsy-proven persistent disease should be re-evaluated in 8 to 12 weeks and if regression is seen, continued observation and re-evaluation in 3-month intervals with yearly CT scans is appropriate. If there is no regression or there is progression of disease, the patient should be restaged and APR offered if the disease is locoregional. Distant failures of epidermoid cancer are responsive to radiation therapy, and up to 30% of patients respond to second-line chemotherapy. Therefore, as a minimum, chest radiography, LFTs, and pelvic CT are recommended every 6 to 12 months for 2 to 3 years after initial therapy. Patients with anal margin cancers should have careful, close follow-up, given the indolent nature of these tumors and the benefits of further local therapy.

Anal Intraepithelial Neoplasia

AIN is a term used to describe squamous intraepithelial lesions (SILs) of the anus. This is an increasingly prevalent condition associated with HPV infection and condylomata that can occur both externally on the perianal skin and internally within the anal canal. Dysplasia in SILs may be low grade or high grade (HSIL); the latter is an intermediate stage in the malignant transformation to SCC of the anus. Anal HSIL represents cytopathologic and histopathologic findings that had been referred to as AIN II/III, severe dysplasia, carcinoma in situ, or Bowen disease, in the past. The presence of HPV infection is the principal risk factor for anal neoplasia. Cofactors include anal-receptive intercourse and immunocompromise. Paralleling observations in the cervix, infection by oncogenic strains of HPV are causally related to the development of the precursor lesion, HSIL, and later of anal cancer. Under the microscope, cervical SIL and anal SIL are virtually indistinguishable. The anatomical region at risk includes the anal transition zone and the distal rectum extending up to 8 cm proximal to the dentate line where immature

squamous metaplastic cells are the most susceptible to oncogenic HPV, although the nonkeratinizing and keratinizing squamous epithelium of the surrounding tissues are also susceptible. There is also morphologic and histologic similarity between cervical and anal cancer.

The populations at greatest risk for AIN are the same as those for anal cancer. Natural history studies have demonstrated that in HIV-negative men who have sex with men (MSM), the 4-year incidence of HSIL was 17%. It is higher in HIV-positive men, with receptive anal intercourse, the presence of condylomata, multiplicity of HPV serotype infections, injection drug abuse, cigarette smoking, depressed host immunity, and the presence of cervical, vulvar, or penile neoplasia.

Treatment

Patients with anal SIL often present with minor complaints related to anal condylomata, hemorrhoids, or pruritus ani. Physical examination may reveal anything from typical condylomatous lesions to normal-appearing anal and rectal mucosa. The perianal skin and the entire surgical anal canal, as defined by the AJCC and by the World Health Organization, as extending through the length of the internal anal sphincter from the anal verge (2 to 4 cm in women, up to 6 cm in men), should be thoroughly examined. The application of dilute acetic acid allows lesions in the distal rectum, anal canal, and keratinized skin to become more visible. The use of high-resolution anoscopy has also been advocated.

Patients with LSIL typically do not need treatment but should be followed by high-resolution anoscopy every 6 months. Patients with low-volume HSIL external to the anal canal and no history of dysplasia may be treated with topical agents in the office, regardless of risk factors, with surveillance anoscopy. Eradication of dysplasia can be achieved with topical cytokine stimulator imiquimod (Aldara) or antimetabolite 5-FU (Efudex). Patients with large-volume disease are treated in the operating room with a combination of excisional biopsy or cautery destruction under monitored anesthetic care with a standard perianal block. This can be achieved with infrared coagulation (IRC) and photodynamic therapy (PDT). “Mapping” of the lesions can be performed and is a strategy that is safe and well tolerated and has been shown to eradicate HSIL in HIV-negative patients. In HIV-positive patients, recurrence is high and treatment may need to be repeated; however, with close follow-up, transformation to invasive cancer can be prevented.

Bowen Disease

Bowen disease is an intraepithelial SCC (carcinoma in situ or intraepithelial high-grade dysplasia) that develops most commonly in middle-aged women and is often discovered during histologic evaluation of an anal specimen obtained for an unrelated diagnosis. The lesion is raised, irregular, scaly, and plaque like, with eczematoid features. Histologically, large atypical haloed cells (Bowenoid cells) are seen that stain periodic-acid–Schiff negative. Although it has previously been believed to have an association with other invasive carcinomas, the evidence for this is weak. The risk of progression to invasive cancer has been reported to be approximately 10%. Bowen disease has traditionally been treated with random biopsies and wide excision with flap reconstruction. However, even if normal tissue is sacrificed to obtain clear margins, the recurrence rate is 23%, and the patient may still be at risk for cancer development. This aggressive approach is associated with complications such as anal stenosis and fecal incontinence. Thus, the extent of excision is typically only to grossly normal tissue.

Bowen disease is histologically and immunohistochemically indistinguishable from anal HSIL and has also been associated with HPV infection. There is increasing agreement that Bowen disease and anal HSIL should be treated in a similar fashion. Local recurrence may occur, but re-excision provides excellent local control. Other therapeutic modalities include topical 5-FU cream, topical imiquimod, PDT, radiation therapy, laser therapy, and combinations of these. Published reports are generally small series with limited follow-up, but there has been anecdotal success with each approach, and all options should be kept in mind for challenging cases.

Paget Disease

Paget disease is an intraepithelial adenocarcinoma that occurs mostly in elderly women. The lesion (a well-demarcated, eczematoid plaque) is usually characteristic; however, morphologic variations can occur, making the diagnosis difficult by inspection alone. The diagnosis is made histologically by the presence of large, vacuolated Paget cells, which stain periodic-acid–Schiff positive (from high mucin content). There is some evidence for the association of perianal Paget disease with other invasive carcinomas, but this relationship is not as strong as that seen with Paget

disease of the breast. Invasion can develop in these lesions, and the prognosis is poor in those cases. Perianal Paget disease should be treated with wide local excision.

Anal Melanoma

Primary melanoma of the anus or rectum is a rare tumor, accounting for 0.4% to 1.6% of all melanomas and less than 1.0% of all anal canal tumors. The overall prognosis for patients with anorectal melanoma is very poor. Several reports in the literature have shown 5-year survival rates that are less than 25% and the median survival time is about 15 months. Mucosal melanoma is further discussed in Chapter 3. This discussion focuses on anal melanoma.

Pathologic Characteristics

The primary tumor may arise from the skin of the anal verge or the transitional epithelium of the anal canal. Inguinal nodal metastases are common at presentation. Prognosis is related to tumor thickness, as with cutaneous melanomas.

Diagnosis

Patients most commonly present with rectal bleeding. The incidental finding of a mass on digital examination may also lead to a workup that establishes the diagnosis. Melanoma may be an incidental pathologic finding after hemorrhoidectomy. Physical examination should include evaluation of the rectal mass and palpation of the inguinal nodes. Radiographic staging should be performed as for melanomas elsewhere.

Treatment

Historically, APR has been the treatment of choice, but high failure rates have questioned the benefit of this radical approach. Wide local excision with at least 2 cm of normal surrounding tissue and sentinel lymph node biopsy of the inguinal lymph nodes is now performed whenever possible, reserving APR for large bulky tumors that cannot be locally excised. Therapeutic inguinal node dissection or external radiation therapy is indicated for nodal disease. Using this approach with hypofractionated adjuvant radiation therapy (30 Gy in five fractions) to the primary site and nodal beds, MDACC has reported a 5-year actuarial survival of 31%, local

control rate of 74%, and a nodal control rate of 84% in 23 patients after a median follow-up of 32 months. Patients presenting with unresectable disease can be treated with neoadjuvant chemo/immunotherapy. Responders can be offered transanal excision or APR with postoperative radiation therapy with or without additional chemotherapy. Nonresponders can be offered palliative surgery.

Anal Adenocarcinoma

Adenocarcinoma of the anal canal is a rare malignancy representing less than 20% of all anal cancers with limited data regarding treatment and outcomes. In a recent retrospective consecutive cohort study at MDACC, the OS and recurrence outcomes were evaluated in 34 patients identified with anal adenocarcinoma. Six patients underwent palliative treatment and in the remaining 28 patients, 13 (46%) were treated with local excision followed by radiotherapy or chemoradiotherapy. Fifteen patients (54%) underwent radical surgery and neoadjuvant or adjuvant chemoradiotherapy. Median DFS was 13 months after local excision and 32 months after radical surgery. OS at 5 years was 43% for patients treated with local excision and 63% for patients treated with radical surgery. High risk for distant failure emphasizes the need for effective adjuvant therapeutic regimens.

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13 Hepatobiliary Cancers

Rebecca A. Snyder and Jean-Nicolas Vauthey

INTRODUCTION

This chapter outlines treatment approaches to the major hepatobiliary cancers, addresses issues of anatomy, and describes preoperative preparation and the operative approach. For each disease type, the current literature is reviewed to provide an explanation of epidemiology, pathology, clinical presentation, diagnosis, staging, and issues regarding surgical and multimodality therapy.

SURGICAL ANATOMY OF THE LIVER

Hepatic anatomy is highly variable. A description of the major arterial variations is beyond the scope of this chapter; however, an overview of relevant hepatic anatomy essential to the discussion of resection options for hepatic tumors is provided. On the basis of the portal segmentation, eight separate anatomical segments of the liver can be identified, first described by Couinaud in 1957. This predominantly portal segmentation of the liver provides the surgeon with an anatomical approach to the liver, such that any of the eight segments can be resected while preserving the vascular inflow, venous outflow, and biliary drainage of the remaining segments.

The right liver typically comprises two-thirds of the total liver volume (TLV), and the left liver one-third. The caudate lobe (segment I), which is a single anatomical unit, represents approximately 1% to 2% of the TLV. Three segments comprise the caudate lobe: the caudate process, paracaval caudate, and Spiegel's lobe. The caudate lobe has highly variable biliary and portal anatomy, as well as its own venous drainage, with short veins draining directly into the vena cava.

The right liver can be divided into the right anterior and posterior sectors, and the left liver divided into the lateral and medial sectors. The

right anterior liver is subdivided into segment V inferiorly and segment VIII superiorly, and the right posterior liver is subdivided into segment VI inferiorly and segment VII superiorly. The left lateral liver is subdivided into segments II and III, and the medial left liver is known as segment IV (Fig. 13.1).

Three major hepatic veins are typically found: the right hepatic vein, which drains the right liver (segments V to VIII); the middle hepatic vein, which drains segment IV; and the left hepatic vein, which drains segments II and III. The left hepatic vein crosses the left lateral liver transversely, between segments II and III. The middle hepatic vein defines the main plane, or the division between the left and right livers, which is the plane defining the right or left hepatectomy resection lines.

It is essential that surgeons understand the many anatomical variations of the liver that can be identified on preoperative cross-sectional imaging and intraoperative ultrasound (IOUS). Surgical techniques, including the Glissonian approach or dissection along the fibrous sheath that surrounds the portal triads, may enable the surgeon to identify important elements of the anatomy intrahepatically, and thereby minimize the risk of injury to the remaining liver after resection of anatomical segments. IOUS is essential for safe liver surgery and permits real-time identification of the intrahepatic anatomy.

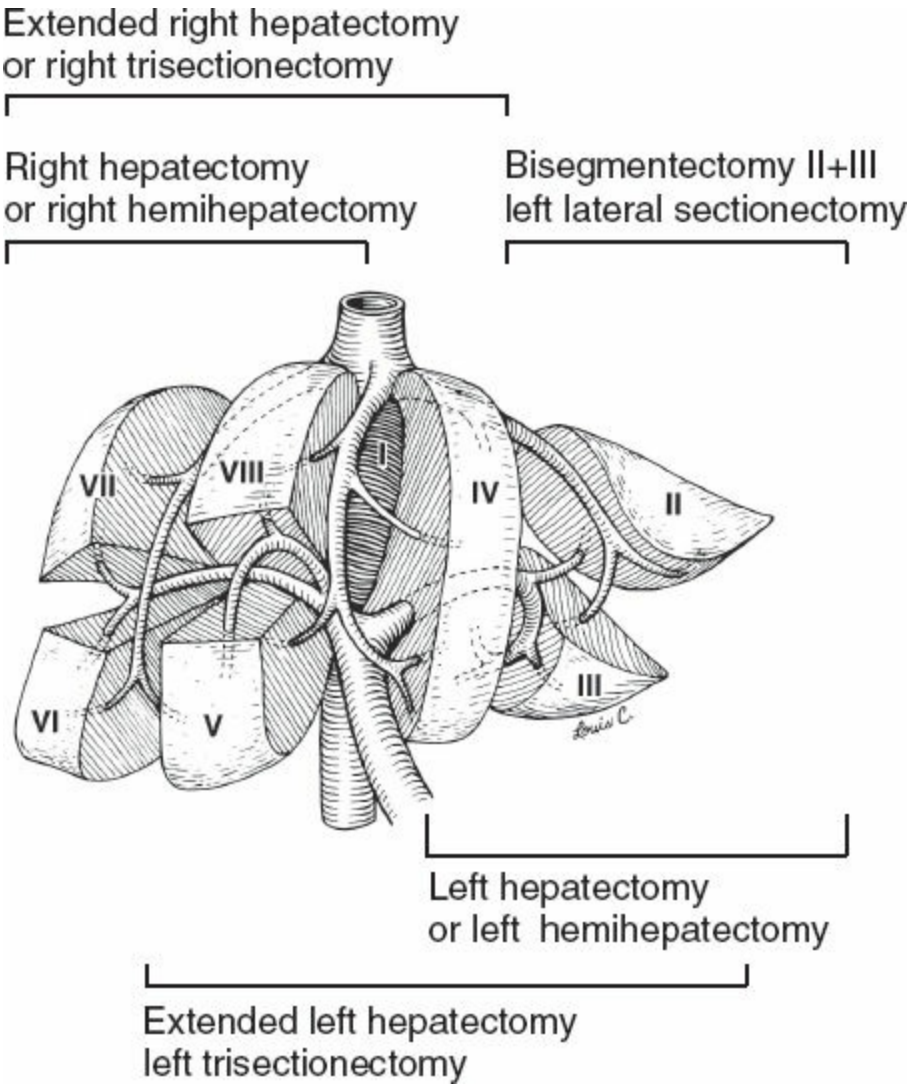


Figure 13.1 Segmental liver anatomy as originally described by Claude Couinaud, with the terminology that should be used to describe liver resection according to the Brisbane 2000 International Consensus Conference. (Adapted from Abdalla EK, Denys A, Chevalier P, et al. Total and segmental liver volume variations: implications for liver surgery. *Surgery* 2004;135:405, with permission.)

TERMINOLOGY FOR HEPATIC RESECTION

Terminology for hepatic resection has changed over time. Accordingly, the Brisbane 2000 International Conference was held to establish a consensus on terminology used for liver resection. That revised terminology is used throughout this chapter (Fig. 13.1).

The terminology for hepatectomy is as follows: (a) resection of the right liver (or segments V to VIII) is termed a right hepatectomy or right hemihepatectomy; (b) resection of the left liver (or segments II to IV) is

termed a left hepatectomy or left hemihepatectomy; (c) resection of the left lateral liver (or segments II and III) is termed a bisegmentectomy II + III or a left lateral sectionectomy; and (d) extended right hepatectomy, or right trisectionectomy, is the resection of segments IV to VIII, whereas extended left hepatectomy, or left trisectionectomy, is resection of segments II to V and VIII.

PREDICTING LIVER REMNANT FUNCTION

Liver Volume Determination

Careful analysis of outcome based on liver remnant volume stratified by underlying liver disease has led to recommendations regarding the safe limits of resection. The liver remnant to be left after resection is termed the future liver remnant (FLR). For patients with normal underlying liver, complications, extended hospital stay, admission to the intensive care unit, and hepatic insufficiency are rare when the standardized FLR is >20% of the TLV. For patients with tumor-related cholestasis or marked underlying liver disease, a 40% liver remnant is necessary to avoid cholestasis, fluid retention, and liver failure. Among patients who have been treated with preoperative systemic chemotherapy for more than 12 weeks, FLR >30% reduces the rate of postoperative liver insufficiency and subsequent mortality (Fig. 13.2).

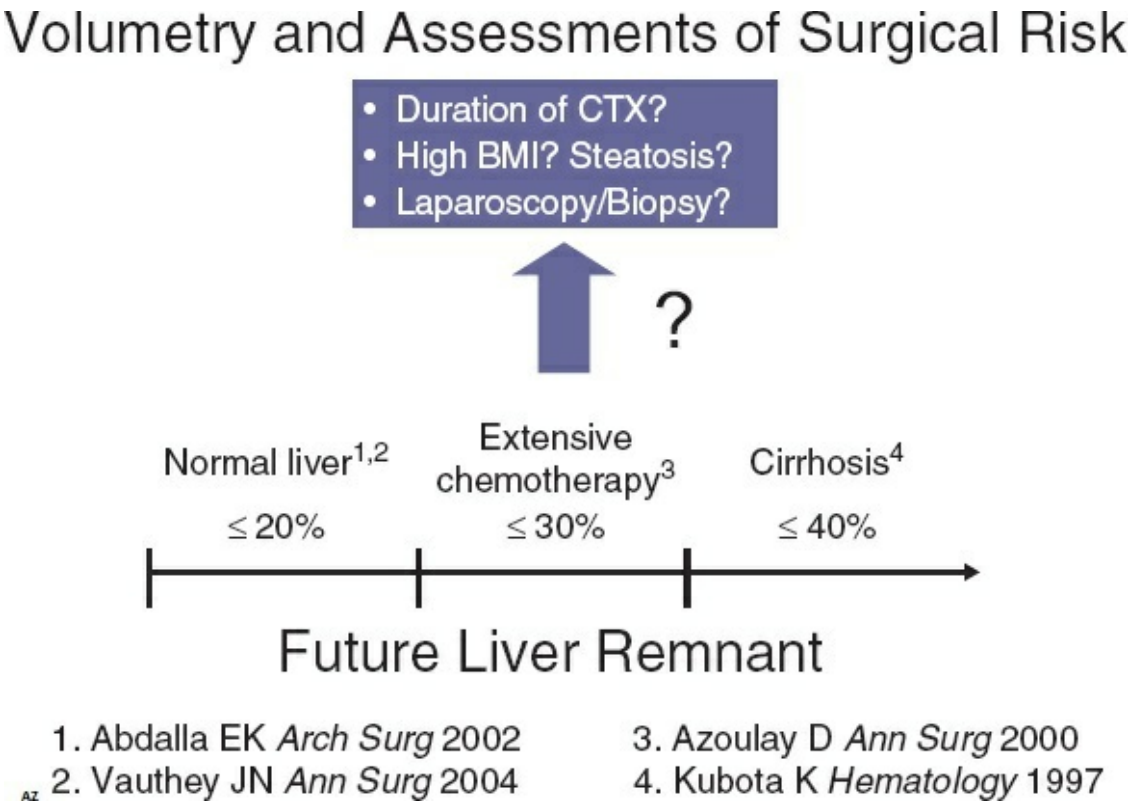


Figure 13.2 Diagram of the future liver remnant required for hepatectomy depending on the parenchymal quality and any pre-existing liver injury. CTX, chemotherapy; BMI, body mass index. (Adapted from Tzeng CW, Vauthey JN. Liver anatomy, physiology, and preoperative evaluation. In: Zyromski NJ, ed. *Handbook of Hepato-Pancreato-Biliary Surgery*. 2015, with permission.)

When the liver remnant is normal or has only mild disease, the volume of liver remnant can be measured directly and accurately with three-dimensional computed tomography (CT) volumetry. However, inaccuracy may arise because the liver to be resected is often diseased, particularly in patients with cirrhosis or biliary obstruction. When multiple or large tumors occupy a large volume of the liver to be resected, subtracting tumor volumes from liver volume further decreases accuracy of CT volumetry. The calculated TLV, which has been derived from the association between body surface area (BSA) and liver size, provides a standard estimate of the TLV. The following formula is used:

$$\text{TLV (cm}^3\text{)} = -794.41 + 1267.28 \times \text{BSA (square meters)}$$

Thus, the standardized FLR (sFLR) volume calculation uses the *measured* FLR volume from CT volumetry as the numerator and the

calculated TLV as the denominator:

$$\text{Standardized FLR (sFLR)} = \text{measured FLR volume/TLV}$$

Calculating the standardized TLV corrects the actual liver volume to the individual patient's size and provides an individualized estimate of that patient's postresection liver function. This approach has been validated and used at the MD Anderson Cancer Center. In the event of an inadequate FLR prior to major hepatectomy, preoperative liver preparation may include portal vein embolization (PVE), which will be discussed in detail in the following section.

Portal Vein Embolization

PVE is a preoperative procedure designed to increase the safety of major liver resections. The portal flow is diverted from the liver segments to be resected to the FLR resulting in hypertrophy of the FLR prior to resection. PVE was refined by Makuuchi after Kinoshita observed that embolization of the portal vein (PV) to prevent tumor extension led to hypertrophy of the contralateral liver. Since then, PVE techniques and indications have been standardized to increase the safety of major hepatectomy in patients with both normal and diseased livers.

Although several different approaches to embolization have been proposed, at the MD Anderson Cancer Center, we use the percutaneous ipsilateral approach to avoid puncturing or injuring the liver remnant. Using spherical microspheres followed by larger coils, the portal branches supplying the entire tumor-bearing liver, including segment IV (if this is to be resected), are occluded. This procedure diverts portal flow to the FLR. Hypertrophy occurs quite rapidly, and the normal liver can be reassessed by volumetry within 3 or 4 weeks. However, hypertrophy may occur more slowly in cirrhotics, diabetics, and patients with other types of chronic liver injury; therefore, an interval of 5 or 6 weeks may be required to achieve the desired degree of hypertrophy.

The kinetic growth rate (KGR), or the degree of hypertrophy at initial volume assessment divided by the number of weeks elapsed after PVE, has recently been demonstrated to be a better predictor of postoperative morbidity and mortality after liver resection, compared to sFLR. A KGR of <2% per week versus ≥2% correlates with higher rates of hepatic insufficiency (21.6% vs. 0%; $P = 0.0001$) and liver-related 90-day

mortality (8.1% vs. 0%; $P = 0.04$) (Fig. 13.3).

Attention to the liver remnant, systemic volumetry for major resection, use of PVE, and measurement of KGR based on carefully prescribed indications has enabled very safe extended hepatic resection in patients with normal liver function and major hepatectomy in patients with underlying liver disease.

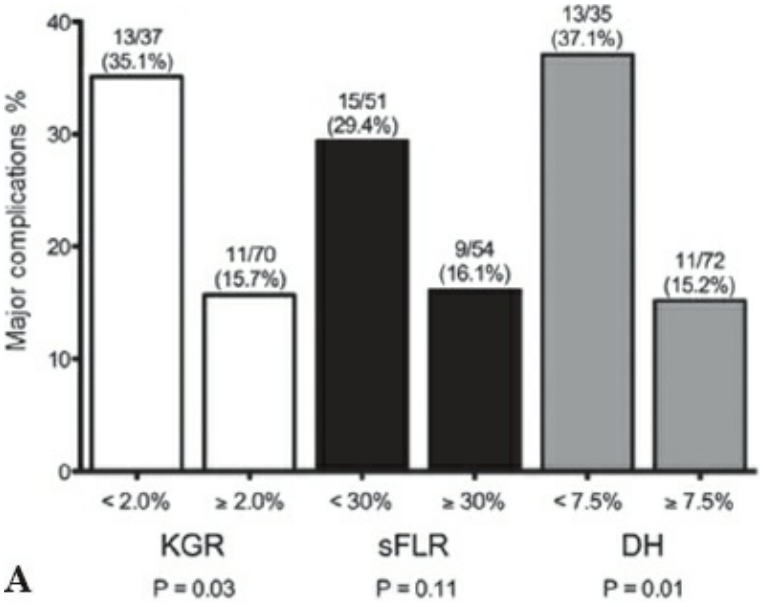
Patients requiring an extended right hepatectomy often have inadequate sFLR and require preoperative PVE (Fig. 13.4). In a recent study by Shindoh et al. of 265 patients undergoing extended right hepatectomy, 52.5% ($N = 139$) had inadequate sFLR and underwent preoperative PVE. Of these, 62.6% ($N = 87$) underwent curative resection, increasing the resection rate from 46.2% at baseline to 79.2% following PVE. Outcomes, including complication and mortality rates as well as disease free and overall survival, were equivalent among the PVE and non-PVE groups.

Among patients with HCC and Child's A cirrhosis secondary to underlying viral hepatitis or alcoholic fibrosis, PVE is indicated to achieve sFLR of >40%. Because the rate of liver regeneration may be slower in these patients, sequential use of transarterial chemoembolization (TACE) and PVE can prevent tumor progression during liver regeneration prior to resection. A recent study by Ogata et al. demonstrated that sequential TACE and PVE leads to improved FLR regeneration rates and DFS when compared to PVE alone in patients with HCC and cirrhosis. At the MD Anderson Cancer Center, direct PV pressure measurement is performed routinely prior to PVE in order to avoid performing PVE in patients with occult portal hypertension.

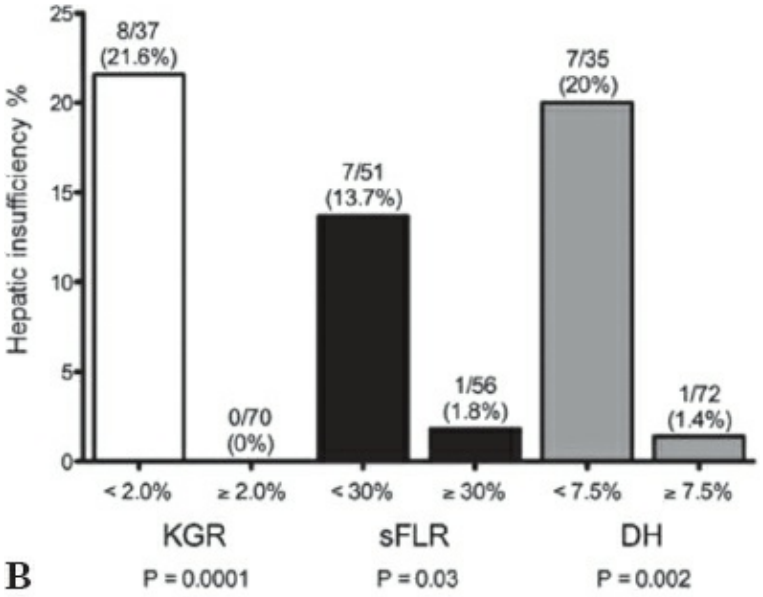
Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy

The technique of associating liver partition surgery with PV ligation for staged hepatectomy (ALPPS) has been recently promoted as an alternative to PVE for patients undergoing extended right hepatectomy. With this technique, PV ligation and in situ splitting of the liver along the falciform ligament is performed to induce rapid hypertrophy of the left lateral section. After a short interval (median 9 days; range 5 to 28 days) patients undergo completion hepatectomy. The proposed benefits include early abdominal exploration for intra- or extrahepatic disease that might preclude curative resection as well as a shortened interval of hypertrophy prior to resection. However, major morbidity rates (40%) and liver-related

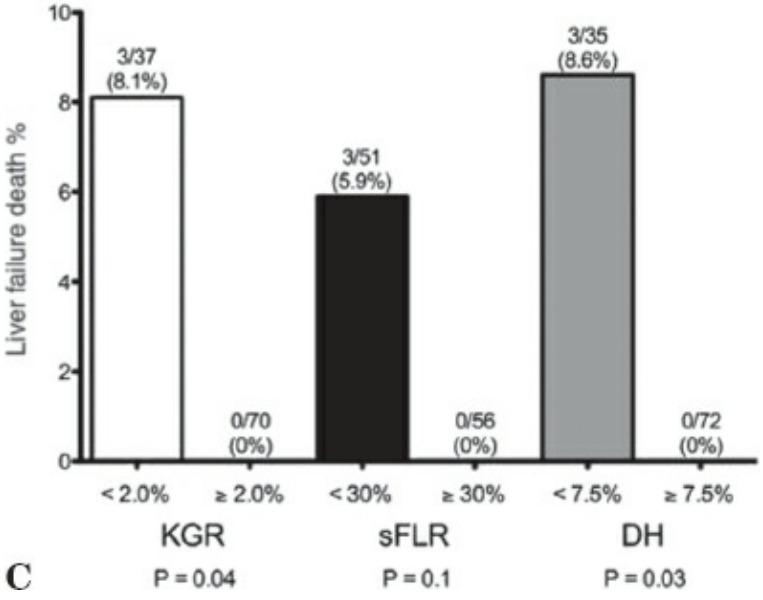
mortality (12%) are significantly higher after ALPPS compared to PVE, and the long-term oncologic outcomes are not yet known. As a result, PVE remains the preferred technique to induce hypertrophy of the FLR when indicated prior to liver resection.


Major complications %
40
30
20
10
0
13/37 (35.1%)
11/70 (15.7%)
15/51 (29.4%)
9/54 (16.1%)
13/35 (37.1%)
11/72 (15.2%)
< 2.0%
≥ 2.0%
< 30%
≥ 30%
< 7.5%
≥ 7.5%
KGR
sFLR
DH
P = 0.03
P = 0.11
P = 0.01

A


Hepatic insufficiency %
25
20
15
10
5
0
8/37 (21.6%)
0/70 (0%)
7/51 (13.7%)
1/56 (1.8%)
7/35 (20%)
1/72 (1.4%)
< 2.0%
≥ 2.0%
< 30%
≥ 30%
< 7.5%
≥ 7.5%
KGR
sFLR
DH
P = 0.0001
P = 0.03
P = 0.002

B


Liver failure death %
10
8
6
4
2
0
3/37 (8.1%)
0/70 (0%)
3/51 (5.9%)
0/56 (0%)
3/35 (8.6%)
0/72 (0%)
< 2.0%
≥ 2.0%
< 30%
≥ 30%
< 7.5%
≥ 7.5%
KGR
sFLR
DH
P = 0.04
P = 0.1
P = 0.03

C

Figure 13.3 Rates of (**A**) major complications, (**B**) hepatic insufficiency, and (**C**) 90-day liver-related mortality based on best cut-off values determined with receiver operating characteristics analysis. DH, degree of hypertrophy; KGR, kinetic growth rate, defined as DH at first volume assessment after PVE divided by weeks between PVE and first post-PVE volume assessment; PVE, portal vein embolization; sFLR, standardized future liver remnant. (Adapted from Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg*. 2013;216(2):201–209, with permission.)

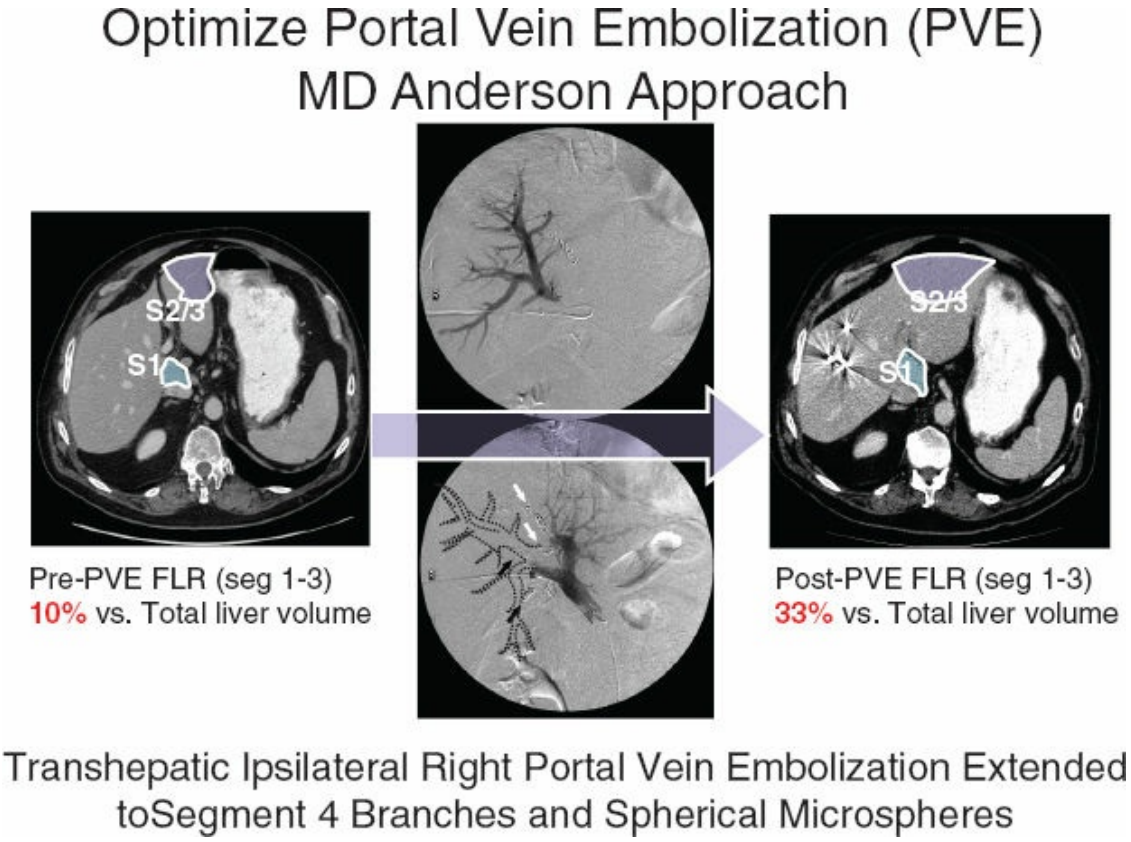


Figure 13.4 Representative images from contrast-enhanced computed tomography of the liver before and after right portal vein embolization (PVE) extended to segment IV resulting in increase of the standardized future liver remnant (sFLR) from 10% to 33%. Portogram captured during PVE shows contrast in the right portal vein and its branches before PVE (*top image*) and contrast in the main and left portal veins, except segment IV branches, after PVE (*lower image*). Coils in segment IV branches are marked with *white arrows,* and the embolized right portal vein

is outlined with *dashed lines. Black arrows* indicate anterior and posterior branches of the right portal vein. (Adapted from Shindoh J, Madoff DC, Aloia TA, et al. Preoperative portal vein embolization: Technique and results. In: Jarnigan W, ed. *Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas*, with permission.)

METASTASES TO THE LIVER

Most liver metastases originate from gastrointestinal primary tumors, and of these, most are from the colon and rectum. In general, 5-year survival is rare among patients who undergo resection for noncolorectal metastases to the liver. The exceptions are selected patients with neuroendocrine tumors, Wilms tumor, and to a lesser extent, renal cell carcinoma; 5-year survival rates of 40% to 70% have been reported after resection in these cases. Hepatic resection may also provide excellent palliation in selected patients with hormone-secreting neuroendocrine tumors. Given that the vast majority of liver metastases considered for resection are secondary to colorectal primary tumors (CRLM), the remainder of this discussion is focused on their management.

Epidemiology and Etiology

Colorectal cancer represents the third most common type of cancer for both men and women in the United States, with an estimated incidence of 135,000 cases per year. Approximately 80% of the patients will have malignancies that are amenable to surgical cure, but approximately 20% of the resected cancers will recur within 5 years. Only 20% of these recurrences will be solely or predominantly in the liver, and fewer still will be amenable to surgical resection. It has been estimated that 15,000 to 20,000 patients per year are potential candidates for resection of their liver metastases.

Clinical Presentation and Diagnosis

In the vast majority of patients, metastases to the liver are found during routine postoperative carcinoembryonic antigen (CEA) screening or radiologic imaging after resection of a colorectal primary tumor. Patients with increasing CEA levels should undergo thorough diagnostic evaluation, including contrast-enhanced CT scan of the chest, abdomen,

and pelvis. A slowly increasing CEA level usually indicates local or regional recurrence, whereas a rapidly increasing CEA level suggests hepatic metastases. Overall, 75% to 90% of patients with hepatic colorectal cancer metastases have an increased CEA level.

Preoperative Staging

High-quality imaging is critical to assessment of CRLM resectability. We favor CT scanning almost exclusively at our institution; our published survival rates are equal to the best reported for resection of metastases from colorectal cancer, validating this approach. CT not only permits assessment of extrahepatic structures, but also accurately provides for liver volumetry, accurate localization of the tumors within the liver, and accurate lesion detection. Multiphase, thin-cut, spiral, hepatic CT is our modality of choice, and the information thus gained has been superior to that afforded by MRI and other approaches. MRI is useful in patients with metastases poorly visualized on CT and in patients with a significant degree of underlying steatosis. Some surgeons prefer MRI over CT in patients after PVE because of the lack of scatter artifact.

Diagnostic laparoscopy (DL) has a limited role in staging of CRLM due to several factors. Preoperative imaging is highly sensitive and full exploration by means of DL is often limited due to prior surgery. Although additional findings at DL may change aspects the operative approach, they typically do not lead to abandonment of resection.

Careful prelaparotomy staging must also include colonoscopy to rule out local recurrence as well as CT of the chest. Although [^{18}F]fluoro-2-deoxy-D-glucose PET has been proposed as necessary for staging, no study has shown that PET improves outcome when high-quality cross-sectional imaging is used. Additionally, false-negative PET is common after chemotherapy, limiting the utility of this technique alone.

A Canadian randomized, controlled trial evaluated the effect of preoperative PET-CT versus no PET-CT on the surgical management of patients with resectable CRLM and found that only 8% (N = 21/263) had a change in surgical management after PET-CT. Liver resection rates were similar (91% vs. 92%) in the PET-CT and control groups, and there was no difference in survival between the two groups at median follow-up at 36 months. At this time, the use of routine PET-CT prior to resection of CRLM is not recommended.

Determining Resectability and Operative Planning

The definition of resectable liver metastases has evolved over time. Whereas previous definitions considered the size, number, and location of lesions, colorectal liver metastases are now considered resectable if all of the disease can be completely resected with a negative margin and an adequate FLR remains. Specific recommendations with regard to response to chemotherapy are difficult to make, although progression of liver metastasis during systemic chemotherapy should prompt selection of alternate chemotherapy agents rather than hepatic resection due to the poor outcomes observed in these patients.

The planned hepatic resection should encompass all metastases detectable on prechemotherapy imaging. Benoist et al. showed that a complete radiographic response cannot be equated with a complete pathologic response; in fact, 83% of metastases suggestive of a complete radiographic response harbor viable tumor cells or develop early intrahepatic recurrence. Conversely, patients with imaging suggestive of viable tumor after preoperative chemotherapy may demonstrate evidence of a complete pathologic response at the time of resection. In a series of 767 patients, Adam et al. observed that 4% of patients had a complete pathologic response, but *none* of these patients had a complete radiographic response.

The use of fiducial markers in very small lesions may be considered prior to initiation of chemotherapy in order to preserve localization of the site of disease at the time of resection. A review by Passot et al. of nearly 1,400 patients with resected CRLM between 2005 and 2015 identified 32 patients who underwent fiducial placement in 41 metastatic lesions. Median size was 12 mm and 83% (N = 34) were located >10 mm deep within the liver parenchyma. After receipt of chemotherapy, nearly half (46%) disappeared on cross-sectional imaging. All were treated with resection (N = 31) or ablation (N = 10), and no local recurrences were identified at median follow-up of 14 months.

In cases of bilateral disease, multistage approaches to surgery should be considered. Preoperative systemic chemotherapy can reduce the size and volume of tumors such that all tumor sites can be resected safely and provide long-term survival. At the first stage, wedge or limited resection clears the planned FLR, preserving the major portion of the parenchyma in preparation for resection of the remaining liver. At the second stage, major hepatectomy or extended hepatectomy removes all remaining disease.

Staged resection usually requires interval PVE to increase the volume and function of the FLR after the first-stage resection.

The safety and efficacy of this approach has been recently reported by Passot et al. Of 109 patients who underwent two-stage hepatectomy for CRLM, 82% (N = 89) completed resection. The cumulative rate of major complications during the first and second stages was 15% with 3-year survival of 68%. A recent series reported marked improvement in survival among patients who underwent two-stage resection for CRLM, with 5-year overall of 51% compared to 15% among patients with liver-only disease who had a good response to chemotherapy, but did not undergo resection. Although this difference may be representative of patient selection to some degree, complete resection of disease is associated with an excellent outcome.

Highly selected patients with *resectable* extrahepatic disease—whether limited peritoneal carcinomatosis, minimal hilar lymphadenopathy, or metastatic disease to the lung—can also undergo resection with acceptable survival. Nearly all of these patients have received a significant amount of systemic chemotherapy with either response or stabilization of disease thereby selecting for "favorable" biology.

Additional decision-making is necessary in the setting of *synchronous* liver metastases to determine the order of resection of the primary colorectal cancer and liver metastases. The complexity of the operation necessary to remove the primary tumor and the extent of hepatic resection required will affect decision making because the risk of adverse events from hepatic resection increases when the procedure is associated with extrahepatic surgery. Solitary, small, peripherally located lesions in a healthy, hemodynamically stable patient that can be excised adequately by nonanatomical resection or segmentectomy may be resected at the same time as the primary tumor. Lesions that are larger or that will require a major hepatic resection are best approached during a separate operation.

A study by Reddy et al. of 610 patients who underwent either simultaneous (N = 135) or staged (N = 475) resection of colorectal cancer and synchronous liver metastases found an increased morbidity after staged resection for major hepatectomy (36.1% vs. 17.6%) but similar morbidity for minor hepatectomy (14.1% vs. 10.5%). In this study, major hepatectomy independently predicted severe morbidity after simultaneous resection (HR = 3.4, P = 0.008).

At our institution, patients with synchronous CRLM and an

asymptomatic primary tumor are treated with neoadjuvant chemotherapy followed by resection of the liver disease first. We have found that this results in an earlier recovery due to the fact that infectious complications are less common following liver resection compared to resection of the colorectal primary. Additionally, we consider disease progression in the liver to be the greatest risk to the patient, which is eliminated with resection of the liver disease first. In the specific setting of synchronous liver metastases and rectal cancer, patients are most often treated with neoadjuvant chemotherapy and liver resection, followed by chemoradiation and then resection of the primary rectal cancer.

Survival and Prognostic Factors

Modern reports on series of patients undergoing hepatic resection for CRLM reveal that the 5-year survival rate is 53% to 58%. The 5-year survival rate has improved from earlier reported rates of 25% to 40%, despite the expansion of operative criteria, including resection of larger, more numerous, and bilobar tumors, as well as resection of synchronous CRLM, and resection with CRLM in the presence of limited extrahepatic disease.

Several modern studies have highlighted the improvement in survival over time with the use of improved operative techniques, anesthesia, patient selection, imaging, and chemotherapy. Figueras et al. reported a 5-year survival rate of 53% among patients with resectable CRLM, regardless of tumor size or number and including patients with resectable extrahepatic disease. Choti et al. reported on a series of patients treated between 1984 and 1992 and compared the outcome with that of patients treated at the same institution between 1993 and 1999. They demonstrated a significant increase in the rate of 5-year overall survival, which was 31% in the early group and 58% in the latter group, despite similar rates of perioperative morbidity and mortality.

We subsequently published a report on the largest modern series of patients who underwent resection of CRLMs (Abdalla et al.). Most patients required a major resection (64% underwent a hemi-hepatectomy or extended hepatectomy), and nearly one-fourth of the patients required a procedure in addition to hepatic resection. Despite the progressive improvement in survival after resection of CRLM, most patients (50% to 70%) will have a tumor recurrence after hepatic resection. Several important studies have outlined the key prognostic factors.

An optimal morphologic response, defined as homogeneous low attenuation with a thin, sharply defined tumor-liver interface on postchemotherapy, preoperative imaging has been demonstrated to be predictive of both pathologic response and improved overall survival. This assessment is distinct from RECIST, and is not a measure of downstaging, but rather imaging features representative of pathologic response to chemotherapy. Among 209 patients with CRLM treated with preoperative chemotherapy with either oxaliplatin or irinotecan-based regimens with or without bevacizumab, major pathologic response rates were 92% among patients with an optimal morphologic response compared to 59% among patients with suboptimal response. Additionally, the 3- and 5-year overall survival rates were higher in the group with an optimal morphologic response ([82% and 74%] and [60% and 45%]; $P < 0.001$]). The improved prognosis associated with an optimal morphologic response has also been validated in medical patients with advanced colorectal liver metastases not amenable to resection.

One of the most widely quoted studies to outline prognostic factors is from Fong et al. who evaluated a series of 1,001 consecutive patients who underwent hepatic resection for metastatic colorectal cancer at the Memorial Sloan-Kettering Cancer Center (MSKCC). Seven independent factors were associated with poor outcome: disease at the surgical margin, presence of extrahepatic disease, metastatic disease in the lymph nodes of the primary lesion, a short disease-free interval from resection of the primary tumor to detection of metastases, the number of hepatic tumors, hepatic tumor diameter >5 cm, and an elevated CEA level. These factors contribute to outcome in different degrees, and scoring of these factors is helpful in predicting prognosis after resection, *but not in selecting patients for surgery*.

The notion that a 1-cm margin is necessary to ensure long-term survival has been dispelled. Analysis of nearly 500 patients in a multi-institutional database showed that the pattern and probability of disease recurrence and the rates of disease-free and overall survival were identical in patients with 1-mm and 1-cm resection margins. A recent international multidisciplinary consensus statement on the management of synchronous CRLM advocates for minimal surgical clearance margin of 1 mm.

A study from MD Anderson Cancer Center by Pawlik et al. clarified the importance of a margin-negative resection by examining the site of recurrence after resection for CRLM based on surgical margin status in a

multi-institutional database. Patients with surgical margins positive for tumor cells had an overall recurrence rate of 52%, compared with 39% for patients with negative margins. Only 3.8% of patients had a recurrence at the surgical margin. The recurrence rates were similar in patients with negative margins of 1 and 4 mm (39%), 5 and 9 mm (41%), and ≥1 cm (39%). The majority of patients who had recurrences developed them at an extrahepatic site (66%), whether alone (30%) or with simultaneous intrahepatic recurrence (36%).

In addition to margin status, the pathologic response to preoperative chemotherapy has emerged as an important prognostic factor after resection of colorectal liver metastases. Blazer et al. showed that the 5-year overall survival for patients with no residual tumor cells in the resected specimen is 75% versus 33% for patients whose resected specimens contain ≥50% residual tumor cells (Fig. 13.5).

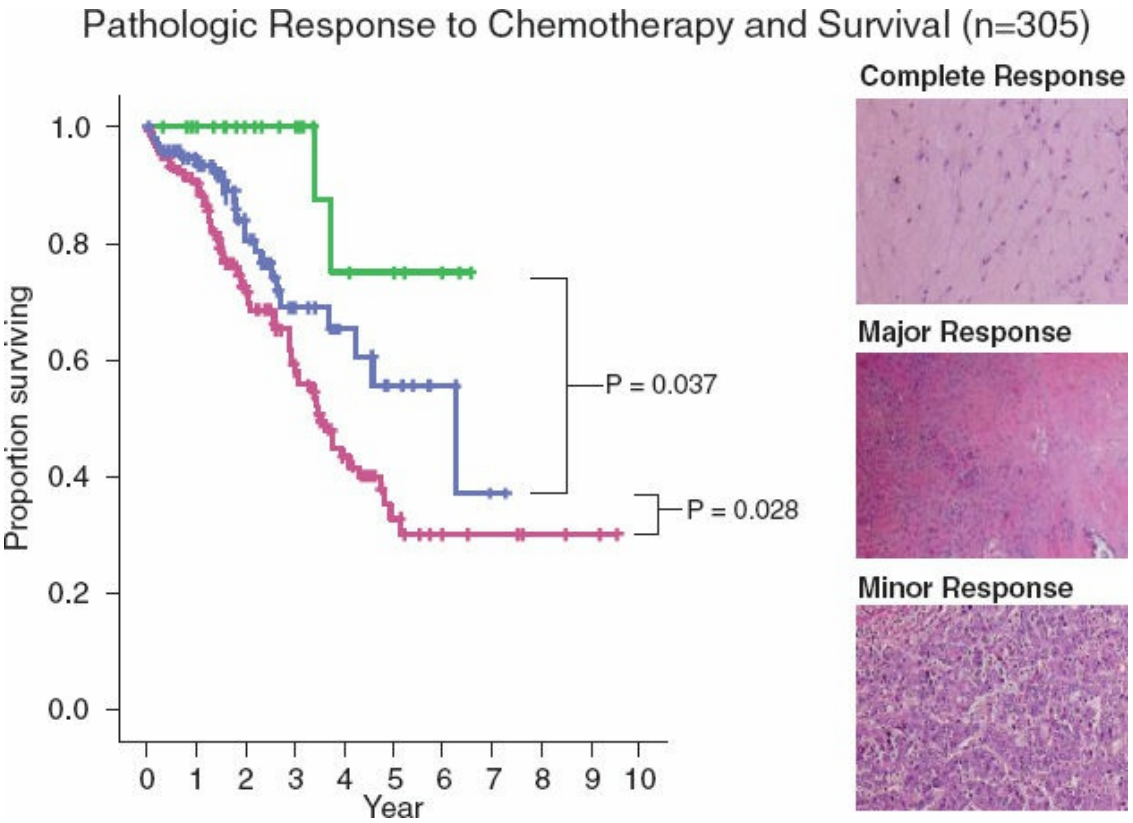


Figure 13.5 Representative photomicrographs of metastases demonstrating complete response (0% residual tumor cells), major response (1% to 49% residual tumor cells), and minor response (≥50% residual tumor cells). Overall survival cures by the degree of pathologic response. (Adapted from Blazer DG, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of

hepatic colorectal metastases. *J Clin Oncol* 2008;25(33):5344–5351, with permission.)

Recently, KRAS mutation status has been found to correlate with outcomes as well. A review by Nash et al. of 188 patients who underwent resection for CRLM identified KRAS mutation among 27% of patients. KRAS mutation was associated with multiple liver metastases, shorter time interval to detection of liver metastases, and was an independent predictor of poor survival after both colon and liver resection (HR 1.9 [95% CI 1.1 to 3.4] and HR 2.4 [95% CI 1.4 to 4.0], respectively). This has been confirmed in a number of subsequent studies, including a study by Vauthey et al. of 193 patients treated with neoadjuvant chemotherapy followed by liver resection at MD Anderson. Three-year OS rates of patients with RAS mutation (including KRAS and NRAS) were 52.2% compared to 81% among wild-type RAS patients (Fig. 13.6). RAS mutation predicted worse OS (HR 2.3, $P = 0.002$) on multivariate analysis as well.

Wild-type RAS has also been shown to be a strong predictor of optimal morphologic response and major pathologic response after neoadjuvant chemotherapy on multivariable analysis compared to RAS mutation (OR 4.4 [95% CI 1.5 to 13.2] and OR 2.6 [95% CI 1.2 to 5.8]). Additionally, RAS mutations have been found to be associated with positive margins in a study by Brudvik et al. of 633 patients, of whom 229 (36%) had mutant RAS (HR 2.4; $P = 0.005$). Altogether, clearly RAS mutation is predictive of more aggressive biology and worse prognosis and may be considered among other factors in the surgical decision making of these patients.

A summary of the multidisciplinary approach to CRLM at MD Anderson is provided in Figure 13.7.

Ablative Therapy

RFA is used widely as a treatment for CRLM. Unfortunately, its use was widespread before consistent indications for ablation were established. Initial, well-designed studies proved the safety, excellent side-effect profile, and efficacy of RFA for CRLM. Studies from our institution and later from Europe and the Cleveland Clinic suggested a 78% 1-year survival rate could be attained by RFA, with 3-year survival at 46%. Unfortunately, >12% of patients had disease recurrence at 1 year. Although RFA provides a modest survival benefit over chemotherapy

alone for CRLM at 4 years (22% vs. 7%), the outcome after RFA is vastly inferior to that after resection in terms of both overall and disease-free survival, whether single or multiple tumors are treated and regardless of tumor size (Abdalla et al). Furthermore, the overall recurrence rate after RFA (84%) in our study was much greater than that after resection (52%); intrahepatic-only recurrence was four times higher with RFA (44%) than with resection (11%), and the frequency of true local recurrences at the RFA site (9%) was 4.5 times that of margin recurrences after resection (2%). Although we ablated only unresectable tumors, these data strongly suggest RFA is inferior to resection as a treatment for CRLM (Abdalla et al).

Subsequent studies have supported these findings. In 2003, Livraghi et al. reported on percutaneous RFA of potentially resectable CRLMs and found a 40% treatment failure rate and a 70% recurrence rate in the 88 treated patients.

Oshowo et al. compared RFA with resection in patients with solitary CRLMs in 2003 and also demonstrated that RFA is inferior to resection as a treatment modality for those with solitary lesions. These investigators reported that RFA outcomes were equivalent to that of resection, however, they reported only a 55% 3-year survival rate for patients with solitary metastases after resection (compared with 53% with RFA), which is inferior to the survival rate achieved by resection in virtually every other series, including our own (which yielded a 5-year survival rate >60%).

RFA may be used as an adjunct to resection, as proposed by Elias et al. and further analyzed by our group. Resection of dominant lesions may be supplemented with RFA of small, residual tumors in the FLR. Unfortunately, our series reveals that this approach is no more effective than RFA alone, and 5-year survival remains <20%. Furthermore, mortality rates are higher with this approach (2.3%) than with extended hepatectomy (0.8% in our series). Finally, as mentioned previously, several studies examining two-stage resection have demonstrated survival rates of 40% at 5 years, again proving the superiority of complete resection over ablation of CRLM.

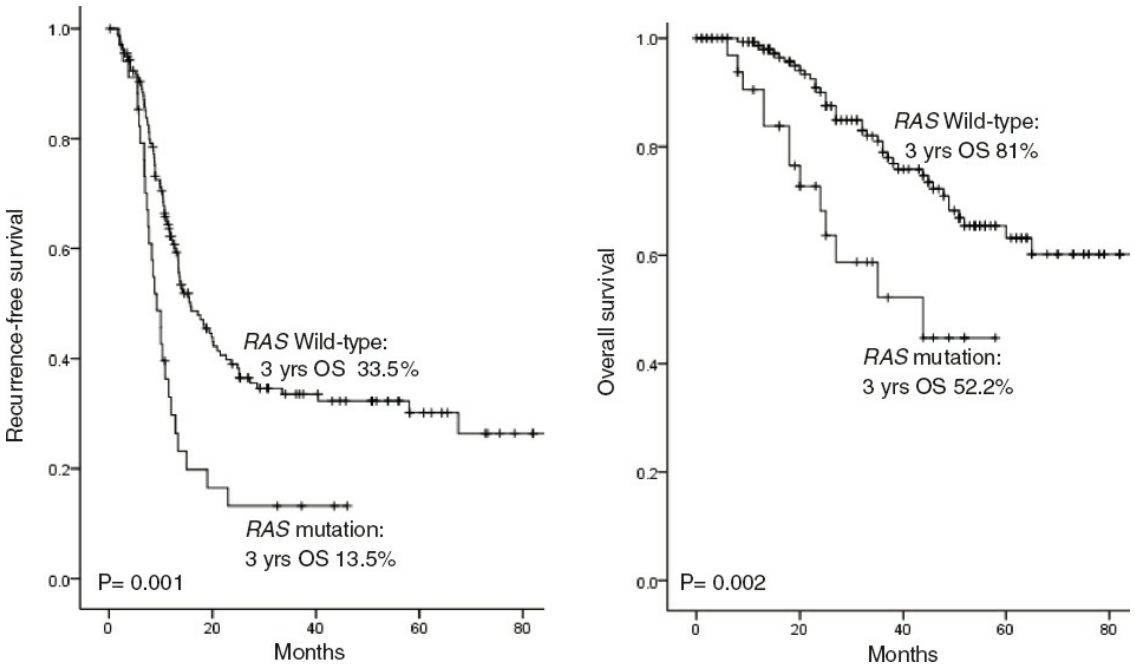


Figure 13.6 Overall survival (OS) and recurrence-free survival (RFS) according to RAS mutation status. (Adapted from Vauthey JN, Giuseppe Z, Kopetz S et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg* 2013;258:619–626, with permission.)

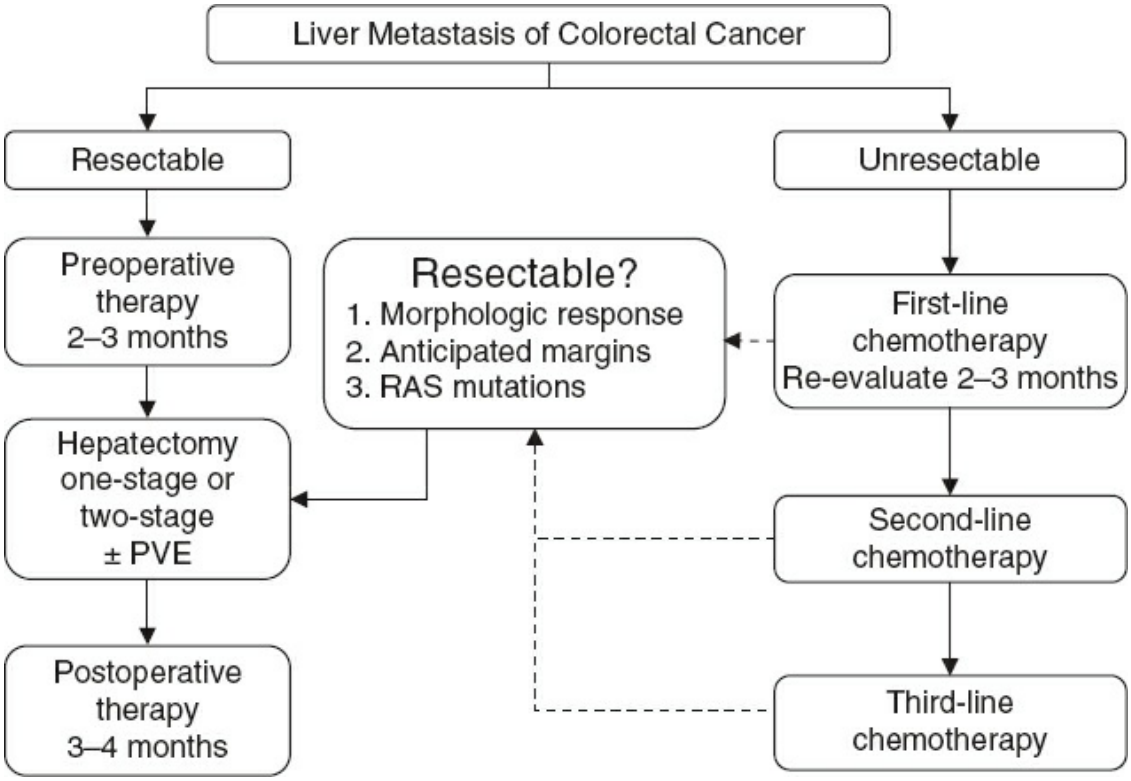


Figure 13.7 Multidisciplinary approach to colorectal liver metastases at MD Anderson Cancer Center. PVE, portal vein

embolization. (Adapted from Shindoh J, Zimmitti G, Vauthey JN, et al. Management of liver metastases from colorectal cancer. In: Chu Q, ed. *Surgical Oncology: A Practical and Comprehensive Approach*. 2015, with permission.)

Ablation is appropriate to treat disease that is unresectable either due to patient comorbidity precluding laparotomy or when margin-negative resection would leave an insufficient FLR, particularly in patients with underlying liver disease. RFA may also have a role in treatment of the ill-placed recurrence after major hepatectomy when repeat resection is considered unsafe.

Thermal injury to the bile ducts can lead to biloma and biliary fistula. Therefore, the potential for ablation can be limited by a tumor's proximity to the confluence of the bile ducts. Typically a 1-cm distance is required. Furthermore, the effect of thermal damage on the FLR can be more extensive than that identified at the time of treatment.

Chemotherapy

Recent advances in chemotherapy for colorectal cancer have dramatically changed the outlook for patients with stage IV disease. The former standard was a combination of 5-FU and leucovorin (LV), which provided response rates from 12% to 40% and median survival of 10 to 17 months.

Subsequently, combination therapies using oxaliplatin or irinotecan (5-FU or LV, with or without oxaliplatin, FOLFOX [5-FU, LV, folinic acid, and oxaliplatin], and FOLFIRI [5-FU, LV, folinic acid, and irinotecan]) have yielded overall response rates >50% and median survival >20 months in the general population of patients with stage IV disease. The addition of biologic agents (including bevacizumab and cetuximab) has increased response rates by 10% and increased median survival to 25 to 27 months.

One of the advantages of preoperative chemotherapy is the potential for rendering unresectable tumors resectable with systemic chemotherapy. Giacchetti et al. and subsequently Adam et al. demonstrated that approximately 13% of patients who present with unresectable CRLM, with or without extrahepatic disease, can undergo resection after chemotherapy.

TABLE 13.1 Chemotherapy-Associated Liver Injury Characteristics

Agent	Liver Changes	Clinical Sequelae
Oxaliplatin	• Sinusoidal dilation • Sinusoidal obstructive syndrome • Microvascular damage	• Increased perioperative transfusions with >6 months of preoperative chemotherapy • Increased complications • Increased overall 90-day mortality (15%) and liver failure-related mortality (6%)
Irinotecan	• Steatosis • Steatohepatitis	

In contrast to administering chemotherapy after all measurable tumor has been resected, the efficacy of a given chemotherapy regimen can be ascertained while the patient is receiving preoperative therapy. EORTC 40983 is the only randomized trial to evaluate the benefit of preoperative chemotherapy (FOLFOX) in the setting of resectable CRLM. Patients in this trial who received perioperative chemotherapy were more likely to complete resection than patients who underwent surgery alone. More importantly the use of perioperative chemotherapy was associated with no difference in OS but a statistically significant improvement in progression-free survival at 3 years in the subset of patients who underwent resection (35.4% vs. 28.1%).

Recently, the long-term results of this trial were reported, and again, patients treated with preoperative chemotherapy had no difference in overall survival compared to patients treated with surgery alone (median survival 61.3 months vs. 54.3 months; $P = 0.34$). However, the trial was not designed or powered to detect a difference in OS. Additionally, more patients in the surgery alone group who developed disease progression received treatment with chemotherapy compared to patients with progression in the perioperative chemotherapy group, which could certainly confound the results. The improvement in PFS did persist among patients who underwent resection, with median PFS of 20.9 months in the perioperative chemotherapy group compared to 12.5 months in the surgery alone group ($P = 0.035$).

In spite of their oncologic benefits, specific chemotherapy agents have been linked to three types of hepatotoxicity (Table 13.1). Steatosis is manifested by a grossly yellow appearance to the liver, and is associated with the use of 5-FU. This type of parenchymal injury does not appear to increase postoperative morbidity. On the other hand, steatohepatitis, characterized by inflammatory features such as hepatocyte ballooning and lobular inflammation, has been associated with the use of irinotecan and

shown to result in an increase in 90-day mortality following liver resection (15% vs. 2% in patients without steatohepatitis). Consequently, major hepatic resection in the setting of steatohepatitis is a relative contraindication. Sinusoidal injury is associated with oxaliplatin, which results in a grossly blue hue to the liver surface. Histologically these changes can be recognized by the presence of hepatic sinusoidal congestion and dilatation. Sinusoidal injury may increase the risk of hepatic resection, but the conflicting nature of the published data suggests that this entity is of lesser clinical concern than steatohepatitis.

Hepatic Arterial Infusion

Regional chemotherapy via hepatic arterial infusion (HAI) was originally investigated for the treatment of hepatic metastases based on the idea that infusion of chemotherapy directly into the hepatic artery would increase drug availability at the site of disease while minimizing systemic toxicity. The best reported response rates using HAI chemotherapy are 50% to 62% in studies that date from the late 1980s. Two European trials using 5-FU in patients with unresectable liver disease failed to demonstrate an improvement in survival and reported high complication rates.

As an adjuvant to liver resection, prospective randomized studies of HAI showed no survival advantage. Furthermore, the treatment failed in the majority of patients, often with extrahepatic spread of disease. This locoregional strategy fails to address occult metastases, which are supplied by the PV, and distant extrahepatic disease, which occurs in the majority of patients with CRLM.

In addition, HAI has been explored as a method to convert CRLM from unresectable to resectable lesions. Although there are no randomized trials, more recent phase II and observational studies have suggested that HAI may allow for conversion to surgery and improved survival in a select group of patients.

In a phase II trial from MSKCC by D'Angelica et al., 49 patients with unresectable liver metastases were treated with combined systemic chemotherapy and HAI. Nearly half (N = 23) achieved conversion to resection at a median of 6 months. In multivariate analysis, conversion to resectability was the only factor associated with prolonged PFS and OS (HR 0.26 [95% CI 0.15 to 0.48] and HR 0.17 [95% CI 0.05 to 0.52]).

A European multicenter study by Levi et al. reported results on 64 patients with unresectable CRLM treated with 5-FU and irinotecan by HAI

in combination with systemic cetuximab. The authors reported a 30% (*N* = 19) macroscopic complete resection rate (R0/R1) with median OS of 35.2 months for those patients, compared to 21.8 months in remaining patients (*N* = 53).

A recent systemic review by Chan et al. of 11 international observational studies designed to evaluate the benefit of floxuridine (FUDR), 5-fluoruracil (5-FU), and/or oxaliplatin HAI in the unresectable CRLM population reported conversion rates ranging from 5% to 34%. Overall survival was improved among patients who converted to resection (median 53 months vs. 16 months). However, the HAI regimen varied significantly across studies, as did the use of concomitant systemic chemotherapy.

The advantage of systemic chemotherapy is that it effectively addresses all metastatic sites, including not only the liver, but also extrahepatic micrometastases. However, HAI may have a role in the conversion of unresectable liver metastases to surgery in select patients. Further studies will be important to better understand the benefit of HAI in comparison to standard systemic chemotherapy.

HEPATOCELLULAR CARCINOMA

Epidemiology

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm in men and the ninth most common in women, accounting for approximately 780,000 cancer cases annually. In the United States, HCC is comparatively rare, with an annual incidence of approximately 6 cases per 100,000 persons in 2010. However, the incidence of HCC in the United States is rising secondary to the increasing prevalence of hepatitis B (HBV) and hepatitis C (HCV) infection.

HCC occurs with greater frequency in regions of the world where viral hepatitis is endemic. There is, however, considerable variation in the prevalence of HCC, HBV, and HCV, depending on a patient's country of origin. It is estimated that one-fourth of patients with HCC in the United States have evidence of HCV infection, and HBV and HCV infections together account for no more than 40% of HCC cases. In contrast, in many Eastern countries where both HBV and HCV infections are endemic, the vast majority of HCC patients are seropositive for either HBV or HCV. Patients from the West (the United States and France) are more likely than

patients from the East (Hong Kong and Japan) to have negative hepatitis serology.

Several other risk factors have been implicated in the development of HCC. Alcohol-related cirrhosis is clearly a risk factor, although the relationship between alcoholic cirrhosis and HCC is confounded by coinciding high rates of viral hepatitis. HCC has also been reported in association with several metabolic disorders, such as hemochromatosis, Wilson disease, hereditary tyrosinemia, type I glycogen storage disease, familial polyposis coli, alpha-1 antitrypsin deficiency, and Budd–Chiari syndrome.

More recently, there is increasing evidence of an association between HCC and nonalcoholic steatohepatitis (NASH), or the presence of inflammation and hepatic steatosis secondary to metabolic syndrome and/or diabetes mellitus. The prevalence of NASH is estimated between 3% and 5% of the U.S. population, with 2.6% annual incidence of HCC among patients with NASH-related cirrhosis. Given the rising rates of obesity within the United States, it is likely that NASH will become an even more prominent risk factor for HCC in the general population.

Pathology

The histologic variations of HCC are of little importance in determining treatment and prognosis, except for fibrolamellar carcinoma which is found in younger patients without cirrhosis, carries a better prognosis than standard HCC, and can be cured by resection. HCC frequently spreads by local extension to the diaphragm and adjacent organs and into the portal and hepatic veins. Metastatic spread occurs most often to the lungs, bone, adrenal glands, and brain.

Clinical Presentation

In countries with systematic screening programs, HCC may be detected at an earlier stage. In Eastern countries, including Taiwan, Hong Kong, Japan, and Korea, HCC is often diagnosed by surveillance abdominal US, helical CT scan, magnetic resonance imaging (MRI), or routine screening of blood for features such as elevated serum alpha-fetoprotein (AFP) before clinical symptoms are apparent.

However, in the United States, where there is no systematic screening for HCC, patients usually present at a later stage, often with upper

abdominal pain or discomfort, a palpable right upper quadrant mass, weight loss, ascites, or other sequelae of portal hypertension. Jaundice is relatively uncommon but is a poor prognostic sign when present. The triad of abdominal pain, weight loss, and an abdominal mass is the most common clinical presentation in the United States. In fewer than 5% of cases, patients present with tumor rupture.

Patients with HCV infection are more often screened and thus tend to present with signs and symptoms of cirrhosis and earlier-stage HCC tumors. Patients with HBV infection or no serologic evidence of hepatitis infection tend to present with larger tumors in the setting of less advanced cirrhosis.

Diagnosis

AFP is increased in 50% to 90% of all patients with HCC, with levels greater than 400 ng/mL usually found in patients with large or rapidly growing tumors. Despite these general correlations, AFP is neither sensitive nor specific for HCC. A patient with a small HCC tumor may have minimal or no elevation of AFP. Moreover, transient increases in AFP may be seen with inflammatory hepatic disease or cirrhosis. Several studies have reported a correlation between AFP elevation, advanced tumor stage, and poor patient prognosis, or an association between highly elevated AFP and metastatic disease; AFP >200 ng/mL in association with characteristic imaging findings is nearly 100% sensitive for HCC.

Several imaging modalities can be used to diagnose HCC, including helical CT scanning, ultrasound (US), and MRI. Both CT and MRI permit dynamic contrast-enhanced imaging. Each imaging modality has advantages and disadvantages. US is an inexpensive screening tool, but its sensitivity and specificity are low, with an overall false-negative rate of more than 50%.

At MD Anderson Cancer Center, helical thin-slice CT scanning is the preferred imaging technique. The liver is imaged in four phases of contrast enhancement: precontrast, early vascular or arterial phases, a portal phase, and a delayed phase. HCCs, hepatic adenomas, and neuroendocrine tumors demonstrate arterial phase enhancement. Enhancement during the portal-dominant phase reveals hypovascular tumors, such as metastatic adenocarcinoma or cholangiocarcinoma (CCA).

DL, although invasive, may have a role in the diagnostic evaluation of some patients with HCC. Patients most likely to benefit from DL are those

with large or ruptured tumors, advanced cirrhosis, or indeterminate nodules in the FLR.

When the diagnosis of HCC is uncertain (e.g., when imaging findings are equivocal and AFP is normal), the histologic diagnosis of HCC can be obtained by US-guided percutaneous needle biopsy or fine-needle aspiration (FNA) biopsy of the mass. Tumor seeding along the biopsy needle track rarely occurs when using modern techniques (<1% of cases). The risks of significant bleeding are low. The risks associated with major resection or transplantation for benign disease may be outweighed by the benefit of FNA biopsy in cases where the diagnosis is uncertain.

Staging

The eighth edition American Joint Committee on Cancer (AJCC) staging system for HCC is shown in Table 13.2. The T classification is based on several pathologic features that impact prognosis after resection: the presence or absence of vascular invasion (either radiographically or microscopically), the number of tumor nodules (single vs. multiple), and the size of the dominant nodule.

A recent study by Shindoh et al. of 1,109 patients with solitary HCC <2 cm found no difference in long-term survival based on the presence of microvascular invasion. Therefore, the new staging system includes tumors less than 2 cm irrespective of microvascular invasion (T1a) and tumors >2 cm without invasion (T1b) within the same T1 category. Similarly, patients with tumors >2 cm with invasion and <5 cm without invasion are both considered T2. HCC with vascular invasion of a major branch of the portal or hepatic vein are designated T4. N1 disease is the presence of any regional lymph node metastasis.

Additionally important is the fibrosis score, which has a significant prognostic value in overall survival. The presence of severe fibrosis of the underlying liver has a negative impact on overall survival, regardless of the T classification. For stage I disease, the 5-year survival rate is 64% with no to moderate fibrosis (F0) and 49% with severe fibrosis or cirrhosis present (F1). The 5-year survival rate for F0 disease is 46% for stage II and 17% for stage III, compared to 30% and 9% for F1 disease. The AJCC staging manual recommends notation of fibrosis but has not yet formally incorporated the F classification into the staging system.

A number of other staging systems have also been developed which incorporate both tumor characteristics and underlying liver function,

including the Okuda staging, The Cancer of the Liver Italian Program (CLIP), and the Barcelona Clinic Liver Cancer (BCLC) systems.

Patient Selection for Surgical Treatment

HCC typically occurs in the background of cirrhosis. Thus, after assessment of a patient's candidacy for surgery based on overall health and comorbidity, assessment of liver function is necessary.

The most widely used classification system for the assessment of liver function is the Child–Pugh (sometimes called the Child–Pugh–Turcotte) system. The parameters measured in this classification system are the total bilirubin and albumin levels, presence or absence of ascites, presence or absence of encephalopathy, and prothrombin time/international normalized ratio (INR). Together, these parameters give a rough estimate of the gross synthetic capacity of the liver. Numerous studies have validated this system as an overall predictor of survival after surgery in cirrhotic patients (Table 13.3). Patients with Child–Pugh class A liver function generally tolerate hepatic resection. Patients with class B liver function may tolerate minor resection, but typically do not tolerate major resection. Patients with class C liver function are at significant risk from anesthesia and laparotomy and are only considered candidates for potential orthotopic liver transplantation (OLT).

TABLE 13.2 American Joint Commission on Cancer Staging System for Liver Tumors, 8th edition (Excluding Intrahepatic Cholangiocarcinoma)

Primary Tumor (T)

TX	Primary cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Fibrosis Score (F)

F0	Fibrosis score 0–4 (no to moderate fibrosis)
F1	Fibrosis score 5–6 (severe fibrosis or cirrhosis)

Adapted from Edge SB. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017, with permission.

The model for end-stage liver disease (MELD) score provides a more objective measure of the extent of liver disease, relying only on quantifiable laboratory values without consideration for subjective physical examination findings such as ascites or encephalopathy. The

MELD score combines serum creatinine, total bilirubin, and INR to calculate an overall score which is most helpful in determining allocation of organs for liver transplant.

TABLE 13.3 Child–Pugh Classification of Hepatic Functional Reserve

Clinical or Laboratory Feature	1 Point	2 Points	3 Points
Encephalopathy (grade)	0 (absent)	1–2	3–4
Ascites	Absent	Slight	Marked
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
International normalized ratio	<1.7	1.7–2.2	>2.2

Each feature is assigned 1, 2, or 3 points; Class A: 5–6 points; Class B: 7–9 points; Class C: 10–15 points.

For anatomically resectable HCC without extrahepatic metastases, our approach to patient selection for major hepatectomy is first based on clinical parameters (performance status, Child–Pugh classification) and degree of portal hypertension. We require a platelet count ≥100,000 and exclude patients with gastric or esophageal varices. Next, systematic determination of the sFLR volume, as described previously, is necessary. PVE is considered on the basis of the previously described criteria. This approach enables resection in cirrhotics with a low incidence of hepatic insufficiency and death. In patients with normal liver function, this approach enables extended hepatectomy with <1% mortality and very low morbidity.

Surgical Resection

The standard treatment for HCC is surgical resection or OLT. However, not all patients with HCC are candidates for surgical resection; of those presenting with HCC, only 10% to 30% will be eligible for surgery, and of those patients who undergo exploratory surgery, only 50% to 70% will achieve resection with curative intent. Patients with cirrhosis may be candidates for limited surgical resection, OLT, or locoregional ablative treatment, depending on the severity of the cirrhosis.

The only absolute criterion that initially renders a tumor unresectable is the presence of extrahepatic disease (and even this exclusion has caveats in

highly selected cases). Other relative contraindications to resection are evidence of severe hepatic dysfunction, inadequate sFLR, and tumor involvement of the main PV or vena cava. Patients with normal liver parenchyma are usually eligible for extensive resection. Patients with compensated cirrhosis may be candidates for minor or major hepatectomy in selected cases. As previously described, when indicated, PVE can be a useful preoperative maneuver in patients with HCC. Palavecino et al. compared the outcomes of patients who did and did not undergo PVE prior to major hepatic resection for HCC. Patients who underwent preoperative PVE for predicted inadequate sFLR had equivalent overall- and disease-free survival, and were less likely to experience major complications than patients who did not undergo PVE. No deaths occurred in the PVE group compared to 18% in the non-PVE group, re-emphasizing the importance of FLR volume analysis.

Once the tumor has been determined to be resectable, the next decision is the extent of liver resection necessary, which depends on tumor size, the number of nodules, the tumor's proximity to vascular structures, and the severity of any underlying liver disease. Formerly, a 1-cm surgical margin was believed to be necessary to ensure long-term survival after resection. However, Poon et al. analyzed outcome based on resection margins in 288 patients who underwent hepatectomy for HCC and found that recurrence rates were similar between groups with narrow (<1 cm) and wide (≥1 cm) margins; only patients with histologically positive margins or satellite nodules separate from the main tumor had relatively higher recurrence rates. The authors noted that patients with margins positive for HCC had a higher incidence of intratumoral microvascular invasion than other patients. In addition, recurrences did not always occur at the margin, but also in the remaining liver distant from the margin, indicating that tumor biology is a more likely determinant of recurrence risk than is a positive margin.

Anatomic resections are preferred over segmental resections, when feasible, based on the extent of underlying liver disease and because of the tendency of HCC to spread along portal tracts. In addition, portal-oriented resections have been shown to be associated with lower morbidity, mortality, and blood loss, as well as higher survival rates, than segmental resections. Regimbeau et al. demonstrated that the overall 5-year survival rate in patients who underwent anatomic resections (54%) exceeded that of those who had segmental resections (35%).

A major pattern of recurrence after hepatic resection is intrahepatic failure with development of new disease. In the setting of underlying viral hepatitis or alcoholic cirrhosis, the tendency of the remaining liver to generate new HCCs partially explains the 30% to 70% recurrence rate after hepatic resection. The most potent predictors of poor survival and high-risk recurrence of HCC are vascular invasion in the tumor and severe fibrosis in the underlying liver. Other correlates with poor outcome are absence of a tumor capsule and high-grade or poor tumor differentiation.

In the event of recurrence after resection, selected patients can be considered for repeat resection, depending on the pattern of recurrence. Both focal, intrahepatic, recurrent tumors, and select adrenal metastases can be resected. Solitary extrahepatic metastases at sites such as the lung, diaphragm, and abdominal wall can also be resected in highly selected patients. In all of these cases, median survival may be as high as 50 months, compared with survival on the order of 10 months for those treated without surgery.

Although some classification systems, such as the BCLC system, and some groups in the United States, propose that patients with large tumors should not be considered for surgery, tumor size alone does not predict biology. In fact, multiple studies have shown that patients with T1 tumors >10 cm in diameter have exactly the same survival pattern after resection as those with tumors <3 cm. We analyzed 300 patients undergoing resection for tumors >10 cm and found that, for the entire group, including some patients with vascular invasion, the 5-year survival was 27% and the 10-year survival was 18%. Perioperative mortality was 5%. There were long-term (≥10 years) survivors among patients who had more than one tumor in which the largest exceeded 10 cm in diameter. The best survival was achieved in patients who had tumors without vascular invasion and who did not have severe fibrosis.

Orthotopic Liver Transplantation

Even after margin-negative resection of HCC, recurrence remains a problem. For these reasons, some have proposed that the only definitive treatment for HCC is orthotopic liver transplantation (OLT) to remove both the HCC tumors and the damaged liver parenchyma.

Once liver transplantation was established as a safe treatment for cirrhosis, it began to be considered as a treatment option for unresectable tumors of the liver, however, early recurrence was common. Improved

outcomes following transplantation for liver failure in patients found *incidentally* to have small HCC suggested that better selection criteria might improve outcomes for liver transplantation performed for HCC. These criteria were formalized after analysis of a study by Mazzaferro et al. who evaluated patients with Child's B or C cirrhosis and either a single tumor ≤5 cm or three tumors ≤3 cm in maximum diameter, who underwent liver transplantation. Survival at 5 years after transplantation exceeded 60%, with disease-free survival exceeding 50%. These criteria, based on the Milan Meeting, were then adopted as the criteria for appropriate selection of patients for OLT for HCC, although the study was small (48 patients) and no tumor had vascular invasion.

On the basis of 70 cirrhotic patients who underwent OLT for HCC during a 12-year period at the University of California–San Francisco (UCSF), some groups now advocate OLT for solitary tumors <6.5 cm, or 3 nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm, commonly referred to as the extended "UCSF criteria."

Nonresectional Locoregional Therapies

For selected patients with HCC confined to the liver whose disease is not amenable to surgical resection or OLT, locoregional ablative therapies can be considered. Although these therapies may also be used in patients with resectable HCC, their efficacy has not been established as equivalent to resection.

The advantages of ablation techniques include destruction of tumors and preservation of a maximal volume of liver, with the potential to combine ablation of small lesions with resection of larger lesions. The major disadvantages of any ablation technique are the limited ability to evaluate treatment margins and the need to obtain negative treatment margins in three dimensions. All ablation techniques have higher local recurrence rates than resection for virtually all tumors. Percutaneous ablation is particularly attractive for treatment of patients with severe underlying liver disease, for treatment of patients with a contraindication to laparotomy, or as a bridge to more definitive therapy, such as OLT.

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) is a treatment administered under US that induces cellular dehydration, necrosis, and vascular thrombosis, causing tumor cell death. Several studies have documented post-PEI

survival rates similar to those obtained with hepatic resection for extremely small tumors in well-selected patients, but HCC recurrence in the liver is frequent, with an incidence of 50% at 2 years; the majority of recurrences are new lesions in distant segments of the liver. Randomized trials suggest PEI is appropriate for tumors ≤2 cm in diameter because it has lower rates of morbidity but equivalent efficacy when compared with other ablation techniques, such as radiofrequency ablation (RFA).

Radiofrequency Ablation

RFA uses heat to destroy tumors. Using US or CT guidance, a needle electrode with an uninsulated tip is inserted into the tumor and delivers a high-frequency alternating current, generating rapid vibration of ions, which leads to frictional heat and, ultimately, coagulative tissue necrosis. RFA can be performed percutaneously, laparoscopically, or through an open incision and is most effective in tumors <3 cm in diameter. Early tumor recurrence after RFA treatment is associated with large tumor size, poor histologic differentiation, advanced stage of presentation, elevated serum AFP, and the presence of hepatitis. RFA cannot be safely performed in tumors adjacent to a segmental bile duct due to the risk of bile leak. For tumors adjacent to a major vessel, the vessel acts as a heat sink, diminishing the efficacy of RFA.

Several studies have suggested that RFA may be effective for unresectable tumors. Two reports have directly compared percutaneous RFA and surgery for treatment of HCC. Hong et al. reported a series of 148 patients who presented with solitary small (<4 cm diameter) HCCs and either no or Child–Pugh class A cirrhosis. The patients selected for RFA either refused surgery or were predicted to have insufficient postoperative hepatic reserve to justify the high operative risks, and were significantly older than those in the comparative resection group. The overall recurrence rates for RFA and surgery were 41.8% and 54.8%, respectively, but the rate of local recurrence was higher in the RFA group (7.3% vs.0.0%). Rates of remote recurrence (defined as distant metastasis or intrahepatic metastasis separate from the original tumor site) and of simultaneous local and remote recurrence were similar between the two treatment groups. The 1- and 3-year overall survival rates were 97.9% and 83.9%, respectively, in the surgery group and 100% and 72.7%, respectively, in the RFA group.

Vivarelli et al. reported 158 patients who underwent either RFA or

surgical resection. The majority of patients in the surgery group had Child–Pugh class A liver function, whereas most patients treated with RFA had class B function. One- and 3-year rates of overall survival were 78% and 33%, respectively, for surgical patients and 60% and 20%, respectively, for RFA patients. Patients with Child–Pugh class A liver function and with solitary lesions, as well as lesions <3 cm in maximum diameter, had significantly higher rates of survival with surgery (overall 3-year survival = 79%) than with RFA (overall 3-year survival = 50%).

The high rate of HCC recurrence following RFA is supported by studies that evaluate the explanted liver following OLT. Mazzaferro et al. observed that among a group of patients with HCC and cirrhosis who underwent RFA followed by OLT, 45% had evidence of residual HCC in the explanted liver. Likewise, Pompili et al. studied a similar cohort and found that 53% of the ablated HCC nodules showed incomplete necrosis. A recent meta-analysis of 13 randomized, controlled trials found higher 3- and 5-year overall survival rates among patients treated with surgery compared to RFA. Consequently, RFA is unattractive as the sole modality for treatment of HCC in patients without evidence of underlying cirrhosis. However, RFA may be the preferred treatment for small HCCs in patients whose tumor cannot be resected safely due to tumor location or due to underlying cirrhosis. For patients who have a tumor recurrence after treatment and who are not candidates for resection, RFA is a satisfactory "salvage technique" and may enable extended remission. Therefore, ablation techniques such as RFA clearly have an important role in the treatment of this HCC patient subset.

Chemotherapy

In general, systemic chemotherapy has little activity against HCC. Single-agent chemotherapy with 5-fluorouracil (5-FU), doxorubicin, cisplatin, vinblastine, etoposide, and mitoxantrone provides response rates of 15% to 20%, and the responses are usually transient. Combination chemotherapy does not seem to improve these results. The most active agent appears to be doxorubicin, with an overall response rate pooled from several trials of 19%.

Investigational regimens for unresectable HCC combine conventional chemotherapy (specifically 5-FU) with immunomodulatory agents, such as alpha-interferon. Preclinical and clinical studies have demonstrated that the two drugs have synergistic activity against colorectal cancer. Despite

its considerable toxic effects, including myelosuppression, the combination of doxorubicin, 5-FU, and alpha-interferon (PIAF) downstaged initially unresectable tumors to a size amenable for resection, and increased the overall median survival rate in an important study by Lau et al. conducted in Hong Kong. The same investigators have reported sufficient tumor regression for subsequent resection, enabling long-term survival after PIAF.

The recent SHARP trial demonstrated that in patients with advanced HCC and preserved liver function (Child's A status), the oral multikinase inhibitor sorafenib was associated with a 3-month increase in median overall survival compared to placebo. However, a recent phase III randomized controlled trial evaluated the efficacy and safety of sorafenib in the adjuvant setting after resection or ablation of HCC and found no difference in recurrence-free survival between sorafenib versus placebo (median 33.3 vs. 33.7 months).

A small phase I trial demonstrated that sorafenib is feasible and tolerable in the posttransplant setting for patients with high-risk HCC. It does not appear that sorafenib provides a benefit in the neoadjuvant setting prior to transplant, however. A phase III trial found no difference in time to progression among patients treated with preoperative sorafenib and transarterial chemoembolization (TACE) compared to placebo and TACE prior to OLT.

Transcatheter Arterial Embolization and Transarterial Chemoembolization

TACE is a combination of intra-arterially infused chemotherapy and hepatic artery occlusion, whereas transcatheter arterial embolization (TAE) omits doxorubicin, the most common chemotherapeutic agent. Chemotherapeutic agents may be either infused into the liver before embolization or impregnated in the gelatin sponges used for the embolization. Lipiodol also has been used in conjunction with TACE because this agent will remain selectively in HCCs for an extended period, allowing the delivery of locally concentrated therapy.

Two randomized control trials have shown that TACE provides a survival advantage for patients with unresectable HCC; thus, TACE is the standard of care for patients who are not candidates for resection, transplantation, or ablation. Furthermore, TACE can be used in combination with ablation or resection or as a bridge to transplantation.

Despite the favorable results of TACE therapy, this treatment modality has limitations. Morbidity rates have been reported to be as high as 23%, especially among patients with HCCs >10 cm in diameter. Moreover, postembolization syndrome, including fever, nausea, and pain, is common. Other adverse reactions, such as fatal hepatic necrosis and liver failure, have rarely been reported. TACE is generally contraindicated in patients with ascites.

Lo et al. presented a randomized controlled trial of TACE and Lipiodol for unresectable HCC in patients with compensated liver failure and in patients with advanced disease (including segmental portal invasion). The chemotherapeutic agent was an emulsion of cisplatin in Lipiodol and gelatin-sponge particles, which was injected through the hepatic artery. The chemoembolization group (40 patients) received a median of 4.5 courses per patient and showed significant tumor response. For the chemoembolization group, the 1-, 2-, and 3-year survival rates were 57%, 31%, and 26%, respectively, while for the control group the rates were 32%, 11%, and 3%, respectively ($P = 0.005$).

Another investigator from the BCLC group performed a randomized trial comparing either TAE or TACE with symptomatic treatment in a much more selected group of patients, who had favorable characteristics compared with those studied by Lo et al. The 112 nonsurgical candidates with HCC and cirrhosis had Child–Pugh class A or B liver functional reserve. The TACE group received doxorubicin combined with Lipiodol and Gelfoam. The trial was stopped when data review demonstrated that chemoembolization yielded survival rates significantly higher than those of conservative treatment. One- and 2-year survival rates were, respectively, 75% and 50% for the embolization group, 82% and 63% for the chemoembolization group, and 63% and 27% for the control group. Since publication of these trials, TACE has secured a role in the treatment of selected patients with HCC.

A recent phase II trial demonstrated safety of TACE using doxorubicin drug-eluting beads (DEBs) for unresectable HCC although the technique has not been proven to be superior to standard TACE.

Radiation Therapy

Historically, external-beam radiation therapy has had limited utility in the treatment of HCC. The dose that can be safely delivered to the liver is approximately 30 Gy; higher doses cause radiation hepatitis and liver

failure. Among patients with unresectable HCC (or other tumors such as cholangiocarcinoma or metastatic adenocarcinoma), tumor-related liver failure—secondary to either biliary obstruction or vascular compromise—is a common cause of mortality. Radiation therapy is therefore most beneficial for patients with unresectable tumors in the hilum or adjacent to the main PV or inferior vena cava (IVC) who cannot undergo local ablative therapies. At the MD Anderson Cancer Center, modified stereotactic radiation techniques including hypofractionation; administration of high, ablative doses to the center of the tumor while sparing nearby organs at risk; and controlling for respiratory motion are utilized to effectively treat unresectable, large liver tumors.

More recently, radioembolization with yttrium-90–labeled microspheres (Y90) has emerged as a local therapy. The advantage of this modality compared to external-beam radiation relates to the delivery of a higher radiation dose that is confined within a more precise liver volume. The target lesion is identified and isolated using catheter-based techniques identical to TACE. The radiolabeled particles are delivered into tumoral arterial feeding vessels. The 25-μm spheres lodge at the distal arteriolar level and the emitted radiation penetrates approximately 10 mm, delivering a dose of about 150 Gy.

A recent US phase II study compared conventional TACE with Y90 radioembolization among patients with BCLC stage A or B HCC. Patients treated with Y90 had a longer time to progression (>26 months) compared to the conventional TACE group (6.8 months), although no difference in overall survival was observed. Although this modality is generally reserved for patients who are not candidates for ablation, resection, or transplantation, radioembolization might also be used to bridge or downstage patients with advanced HCC.

High-dose, hypofractionated proton beam therapy has also been recently demonstrated to provide local control for unresectable HCC in patients with Child's A or B cirrhosis in a multi-institutional phase II trial. In this study of 91 patients with HCC or intrahepatic cholangiocarcinoma, proton therapy resulted in a 94.8% local control rate and 63.2% overall survival at 2 years. Phase III trials investigating proton therapy are ongoing.

SUMMARY

To summarize, patient selection, accounting for the extent of underlying liver disease, is critical when considering resection for HCC. Patients with

normal liver function or Child's A cirrhosis are good candidates for major or minor resection. Minor resection may be considered among patients with Child's B cirrhosis; however, more extensive resection is not typically tolerated. Patients with HCC in the setting of Child's C cirrhosis may be considered for OLT if the Milan criteria are met. Prior to resection for HCC, determination of the sFLR is critical, and PVE is often necessary. Among patients who are not candidates for resection, locoregional therapy such as RFA, TACE, or Y90 radioembolization, may be an effective bridge to transplantation, and in some cases, can result in improvements in time to progression or overall survival. At select centers, stereotactic ablative radiation can be used to treat unresectable tumors at risk for local progression and liver failure. In general, systemic chemotherapy provides little benefit for patients with HCC. Based on the current data, there is a role for sorafenib only in the metastatic setting.

Cholangiocarcinoma

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinomas (ICCAs) arise from the intrahepatic bile ducts and can be grouped according to their growth patterns, which can be mass-forming (MF), periductal-infiltrating (PI), or can grow within the duct lumens (intraductal growth). The MF type presents as a round mass within the liver parenchyma and can recur in the remnant liver after hepatic resection. The PI type of intrahepatic CCA grows longitudinally along the bile duct, often causing an obstruction or stricture. A worse outcome is associated with tumor infiltration of the bile duct serosa, lymph node metastases, and vascular and perineural invasion. ICCAs have a higher propensity to metastasize to regional lymph nodes than perihilar cholangiocarcinomas (PCCAs).

The incidence in the United States appears to be rising, at least in part secondary to the increasing prevalence of nonalcoholic steatohepatitis. However, overall survival rates remain low, with less than 5% overall 5-year survival, and little is known about outcomes related to specific treatment types.

In a recent series by Yamashita et al. of 362 patients treated at the MD Anderson Cancer Center from 1997 to 2015, 160 patients were initially considered to be candidates for surgery, including up-front resection (N = 79) or neoadjuvant chemotherapy followed by resection (N = 43). An additional 38 patients were found to have unresectable disease either due

to intraoperative findings or progression on preoperative chemotherapy. Of the remaining 202 with unresectable disease, most were treated with systemic chemotherapy (*N* = 116), radiation (*N* = 81), or supportive care (*N* = 5).

The most common cause of death was liver failure secondary to local tumor progression. Patients treated with definitive chemotherapy died from liver failure more often (*N* = 71/99, 72%) compared to patients treated with resection (*N* = 14/47, 30%) or radiation (*N* = 18/44, 41%). On multivariable analysis, the only independent predictor of death without liver failure was local therapy (either resection or radiation) (OR 4.11 [95% CI 2.1 to 8.2]). Therefore, we advocate liver-directed therapies for all stages of disease in order to maximize intrahepatic disease control.

Survival rates in this study improved over time among patients treated with local therapies. Although it is difficult to compare outcomes by treatment times due to selection bias, resection appears to provide the best potential for long-term disease-free status in patients with ICC.

PERIHILAR CHOLANGIOCARCINOMA

Epidemiology and Etiology

The etiology of PCCA is unknown. Several diseases are associated with an increased risk, including sclerosing cholangitis, ulcerative colitis, choledochal cysts, and Caroli disease (a congenital disease characterized by multiple intrahepatic biliary cysts). The common cancer-causing factor in these conditions is unclear, although chronic inflammation of the bile duct probably plays a role.

Pathologic Characteristics

Adenocarcinoma is the most common histologic type of biliary cancer; morphologically, PCCA can be classified as papillary (<5% of cases), nodular (20%), or sclerosing (70%). Most papillary tumors are well differentiated and present with multiple lesions within the duct. Virtually all long-term survivors have papillary-type PCCA. Conversely, most sclerosing-type PCCAs are poorly differentiated, and this type is associated with a poor prognosis. A tumor arising at the confluence of the right and left hepatic ducts is termed a Klatskin tumor, following the description of 13 such lesions by Klatskin in 1965.

PCCA is typically classified according to the Bismuth–Corlette classification. This classification defines the longitudinal extension of the tumor and helps define the surgical strategy (Fig. 13.8). Type I tumors are below the confluence of the left and right hepatic ducts without involvement of the "roof" of the biliary confluence. Type II tumors are similar to type I tumors but *extend* to the roof. Type III lesions extend through the intrahepatic bile ducts to involve second-order ducts to the right (type IIIa) or left (type IIIb) only, sparing contralateral ducts. Type IV tumors extend to second-order ducts on both the right and the left. Treatment is defined by location due to the fact that the liver drained by all involved ducts must be resected for cure.

PCCAs are slow growing and most often spread by local intrabiliary ductal extension, peritoneal metastasis, or intrahepatic metastasis. Metastasis to regional lymph nodes occurs less frequently (30% to 50% of cases), and perineural extension occurs as well. Distant metastases are present in approximately 25% to 30% of patients at the time of diagnosis, but hematogenous spread is rare. Lesions of the proximal and middle thirds of the extrahepatic bile duct can compress, constrict, or invade the underlying PV or hepatic artery. In addition, proximal tumors can invade the liver parenchyma. PCCAs will involve the parenchyma of the caudate lobe in as many as 36% of patients; their appearance at this site usually occurs by means of biliary extension through the short caudate ducts that drain to the confluence, although they may emanate from a tumor located near the biliary confluence.

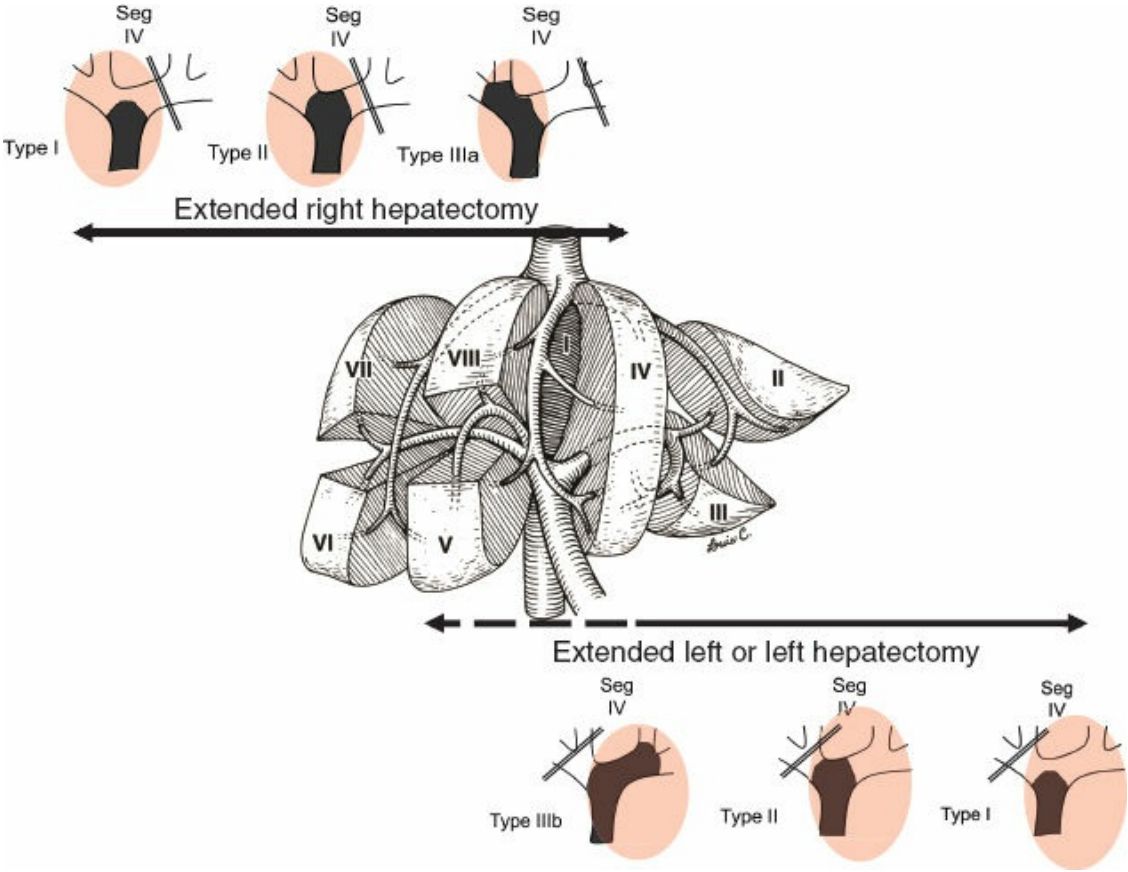


Figure 13.8 Classification of extrahepatic bile duct tumors according to the Bismuth–Corlette system, which describes the common patterns of hilar CCA within the biliary tree. The figure displays the surgical strategy for each tumor type and provides the language used to describe such tumors. Types I, II, and IIIa are treated by extended right hepatectomy, whereas types I, II, and IIIb are treated by left or extended left hepatectomy.

Clinical Presentation

The most common presenting symptoms in patients with PCCA are obstructive jaundice (which occurs in 90% of patients) and itching. Rarely, a very proximal tumor may block a segmental or lobar bile duct without causing jaundice. Other symptoms that may occur are weight loss (29% of cases), vague abdominal pain (20%), fatigue, and nausea. A patient may also present with cholangitis and sepsis resulting from bacterial contamination of the obstructed bile duct. In the case of middle or distal duct obstruction, a distended gallbladder may be palpable on abdominal examination; conversely, hilar PCCA is typically associated with a nondistended gallbladder. In addition to having elevated serum total bilirubin, patients with PCCA will present with elevated alkaline

phosphatase, and possibly elevated tumor markers (carbohydrate antigen 19-9 [CA19-9] and CEA).

Diagnosis

The first radiologic test that should be performed when extrahepatic bile duct obstruction is suspected is US, which can provide information about the level and nature of an obstructing lesion. US can also give information regarding the morphology of the lesions, possible dilation of extra- and intrahepatic bile ducts, PV and hepatic artery patency, and the presence of gallstones and gallbladder dilation.

Further imaging is necessary to delineate the cross-sectional and longitudinal (intrabiliary) extent of the tumor. At MD Anderson, multiphase helical thin-cut CT scanning is used in combination with endoscopic retrograde cholangiopancreatography (ERCP). Helical CT scanning has an overall accuracy of 76% to 100%, and MRI has an overall accuracy of 89% for staging PCCA. We prefer CT because it allows assessment of vascular encasement, cross-sectional assessment of the tumor's biliary extent, and assessment for distant metastatic disease in a single study.

In the absence of distant disease, the precise location of the tumor and its proximal and distal extent must be defined before any intervention is planned. This information can be obtained using ERCP, magnetic resonance cholangiopancreatography (MRCP), or percutaneous transhepatic cholangiography (PTC). Both ERCP and MRCP overestimate the extent of bile duct involvement in about 40% of cases, and both imaging modalities may fail to define the extent of intrabiliary tumor proximally. If the point of obstruction is believed to be proximal to the perihilar region, PTC is the preferred method for defining the biliary tract. PTC also allows brush biopsies of the tumor, external drainage of obstructed biliary ducts, and palliative stent placement when indicated.

Despite improved prelaparotomy imaging, 25% to 40% of patients are found to have unresectable disease at the time of surgery. DL is recommended in most patients with large or extensive hilar tumors because of the frequency of metastases in the peritoneal cavity.

For resectable PCCA, obtaining tissue to confirm the diagnosis of bile duct cancer is not essential and often proves difficult. In most instances, the decision to operate is based on the preoperative radiologic findings, not histologic confirmation. The sensitivity of brush biopsies is poor (well

below 50%), although newer techniques such as endoscopic US-guided FNA of the bile duct may improve diagnostic accuracy. Treatment is guided by anatomical findings (e.g., biliary obstruction, vascular encasement, liver atrophy).

Staging and Anatomical Classification

The eighth edition AJCC staging system provides separate staging for ICCA, PCCA, and extrahepatic cholangiocarcinoma which are presented in Tables 13.4 to 13.6.

RESECTABILITY CRITERIA

The definitive therapy for all extrahepatic bile duct carcinomas is complete resection. Overall resectability rates range from 10% to 85%. Lesions of the lower third of the bile duct have the best rates of resectability by pancreaticoduodenectomy (discussed in Chapter 14); middle-third obstructions of the bile duct are almost always due to gallbladder cancer, which is considered separately. PCCAs are technically more challenging to resect, giving them the lowest rate of resectability among bile duct tumors. Standard criteria used to determine resectability relate to the biliary extent and vascular encasement by the tumor. Involvement of secondary bile ducts necessitates hepatic resection on the side involved. Vascular involvement of the PV or hepatic artery necessitates hepatic resection of the anatomical side involved as well. However, if secondary bile ducts are involved on one side and vascular encasement occurs on the opposite side, complete resection is not possible. Lymph node involvement outside the hepatic pedicle (N2) and distant metastases preclude resection. Intrahepatic CCAs are treated by hepatic resection with tumor-free margins.

Surgical treatment of PCCA is subject to several controversies, which are described briefly: biliary drainage, extent of hepatic and caudate resections, and PV resection (PVR). Other factors in selecting patients for resection, such as patient performance status, are common between this disease and any others, and assessment of the FLR volume is a mandatory part of PCCA treatment because most patients require major or extended hepatectomy with resection of the extrahepatic bile duct.

Studies from our own institution, as well as that of the largest series of patients in the world (from Nagino and Nimura in Japan), show that FLR volume must be considered and PVE used to increase the FLR volume

prior to extended hepatectomy for hilar PCCA. Because the confluence of the bile ducts sits at the base of segment IV, this segment must usually be resected, regardless of whether the tumor is central, to the left, or to the right. Hepatic resection is usually to the right, to include extended right hepatectomy, because 97% of the described variations in biliary anatomy include preservation of a long left hepatic duct. Thus, hilar disease extending even slightly to the left or significantly to the right can be cleared by means of extended right hepatectomy, taking advantage of this long left duct. However, the problem with this approach is the higher risk of liver failure secondary to inadequate FLR even after PVE.

TABLE 13.4 American Joint Commission on Cancer Staging System for Cancer of the Intrahepatic Bile Duct, 8th edition

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Adapted from Edge SB. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017, with permission.

Clearly, disease to the left requires a left hepatectomy, which necessarily includes resection of segment IV or extended left hepatectomy. In general, obtaining a negative margin is more difficult for Bismuth type IIIb tumors involving the left hepatic duct due to the need for biliary reconstruction using the short right hepatic duct. Further, the right hepatic artery may be involved in this scenario, and may require arterial reconstruction. However, Nagino et al. have reported performing an increasing number of extended left hepatectomies, comprising 30% of the total number of hepatectomies for PCCA from 2006 to 2010. Additionally, his group has demonstrated an improvement in overall mortality (from 11.1% from 1977 to 1990 to 1.4% from 2006 to 2010).

On the basis of these principles, we next discuss several controversial issues and provide our recommendations, which attend closely to the principles of preoperative preparation of the patient and liver for surgery.

TABLE 13.5 American Joint Commission on Cancer Staging System for Cancer of the Perihilar Bile Ducts, 8th edition

Primary Tumor (T)	
TX	Primary cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor confined to bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
Stage IVB	Any T	Any N	M1

Adapted from Edge SB. *AJCC Cancer Staging Manual.* 8th ed. New York: Springer; 2017, with permission.

Biliary Drainage

The need for preoperative biliary drainage has been debated at length in the literature, but most consider resolution of jaundice as a critical element in preparing the patient and liver for major hepatectomy. The procedure itself is safe and does not appear to increase operative complications. In a Japanese series by Ebata et al. of 160 patients with PCCA, percutaneous

intrahepatic biliary drainage was performed in 50 of the 52 patients who underwent combined liver and PVR without complications.

At the MD Anderson Cancer Center, we routinely place preoperative biliary drainage catheters to drain the FLR. The liver to be resected is not typically drained unless it is necessary to resolve jaundice. Hyperbilirubinemia impairs liver regeneration and reduces resistance to systemic infection. Hepatic resection in a jaundiced patient is associated with increased rates of mortality (36% vs. 16% for those with bilirubin <2 mg/dL) and complications (50% vs. 15%). Preoperative placement of biliary drainage catheters also facilitates the identification and dissection of the bile duct during surgery.

TABLE **13.6** American Joint Commission on Cancer Staging System for Cancer of the Distal Bile Duct, 8th edition

Primary Tumor (T)

TX	Primary cannot be assessed
Tis	Carcinoma in situ
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5–12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIA	T2	N0	M0
Stage IIB	T2	N1	M0
Stage IIB	T3	N0/N1	M0
Stage IIIA	T1–T3	N2	M0
Stage IIIB	T4	Any N	M0
Stage IV	Any T	Any N	M1

Adapted from Edge SB. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017, with permission.

In a study of 133 patients with hilar cholangiocarcinoma who underwent major hepatectomy, Ribero et al. found a higher rate of preoperative cholangitis among patients treated with endoscopic retrograde biliary drainage as compared to percutaneous transhepatic drainage (64% vs. 13%, $P = 0.002$). Therefore, we typically prefer percutaneous drainage in the preoperative setting.

Finally, the degree of cholestasis in the FLR impacts not only the need for preoperative biliary drainage, but also may impact the threshold to pursue PVE. On multivariate analysis, preoperative cholangitis (OR 7.5, $P = 0.016$) and FLR volume <30% (OR 7.2, $P = 0.019$) predicted postoperative liver failure-related death. Therefore, we advocate PVE in order to ensure FLR >30% among patients with cholestasis.

Extent of Hepatic Resection

Resection of hilar CCA should be performed only when negative surgical margins (R0) can be achieved. Anatomically, resection of hilar cholangiocarcinoma should be considered to include the caudate lobe for two reasons. First, preoperative imaging inadequately defines the precise caudate drainage, which is quite variable among the general population. Second, the boundary between the posterior caudate and the anterior right or left liver is often difficult to appreciate intraoperatively. Attempts at preserving the caudate parenchyma may unintentionally result in incomplete tumor resection. Pathologic examination of resected specimens demonstrates direct invasion of tumor into the liver parenchyma or bile ducts of the caudate lobe in as many as 35% of patients. In addition, the caudate lobe is often the site of tumor recurrence following bile duct resection.

Jarnagin et al. reported a series of 80 patients who underwent resection for CCA; the operative mortality and 5-year survival rates were 10% and 27%, respectively. However, the 5-year survival after resection including hepatectomy (28% with caudate resection) was 37% versus 0% after resection of the bile duct without hepatectomy. Ebata et al. later reported a series of 160 patients, all of whom underwent hepatic resection with caudate resection and reported a similar operative mortality (10%) and 5-year survival (37%), despite the need for portal resection in 52/160 patients.

At the MD Anderson Cancer Center, type I and II PCCAs are treated with extended right hepatectomy or (extended) left hepatectomy along with resection of the caudate process and paracaval caudate. Type IIIa PCCAs are treated with an extended right hepatectomy, along with resection of the caudate process and paracaval caudate. Spiegel’s lobe is resected if the duct is involved. Type IIIb PCCAs are treated with a left or extended left hepatectomy, along with resection of the entire caudate liver.

Type IV lesions previously considered as unresectable are now selectively considered for resection. Several studies have reported OLT as a treatment option for CCA as a part of a multimodality protocol-based approach. The results have been consistently disappointing, with high tumor recurrence rates and low overall survival (5-year survival rate of 23%). The sequence of open laparotomy for staging, intensive chemoradiation, and then OLT has been investigated primarily at the Mayo Clinic (Rochester, MN). Approximately 80% of patients satisfying

the strict entrance criteria eventually undergo transplantation. The 5-year survival for all patients after the start of chemoradiation therapy is 55%, and 71% for those patients who undergo transplantation. Patients entering this protocol need not have biopsy-proven cholangiocarcinoma; instead, the inclusion criteria accommodate for other radiographic and biochemical surrogates. Consequently, the possibility that a proportion of the patients may not have definitively had cholangiocarcinoma prior to initiation of neoadjuvant therapy and subsequent transplantation remains plausible.

Lesions of the lower third of the bile duct do not require hepatic resection, but rather pancreaticoduodenectomy (Whipple procedure). The proximal bile duct should be resected to the point that the surgical margin is negative for tumor. Occasionally, this may require removal of most of the extrahepatic biliary tract with a high hepaticojejunostomy. The operative approach for pancreaticoduodenectomy at the MD Anderson Cancer Center is outlined in Chapter 14.

Lesions of the middle third of the bile duct (termed type 0 tumors by Akeeb and Pitt) are exceedingly rare. Because of these tumors' proximity to the hepatic artery and the PV, these structures are typically involved. When a type 0 tumor is deemed resectable, it is best treated by either hilar resection or pancreaticoduodenectomy. Clinically, most mid-duct obstructions are due to gallbladder cancer.

Limited regional lymphadenectomy is generally indicated for hilar CCAs during extrahepatic bile duct resection to allow for proper staging in order to determine appropriate postoperative therapy and prognosis.

Portal Vein Resection

There are two general approaches to PV invasion when considering resection of hilar CCA. Although some would consider portal invasion a contraindication to resection, long-term survival can be achieved by complete resection, including PVR.

Neuhaus et al. in Germany proposed a systematic approach to PVR, the "no touch technique." It involves PVR in all cases of hilar CCA. Although a better 5-year survival rate was attained with PVR (65%) than without (0%), most patients with PVR underwent right-sided margin-negative resection (which, as described previously, enables a tumor-negative margin because of the long left duct). Furthermore, the operative mortality rate was significant (17%). A second approach was proposed by Nimura et al. and updated by their group in a report from Ebata et al. This group

recommended evaluating portal adherence to the region of the tumor at surgery. They validated their selective PVR approach (used in 52/160 patients) by demonstrating that 69% of those who underwent PVR had microscopic evidence of tumor invasion in the resected PV. Those in this series who did not undergo PVR had a better 5-year survival rate (37%) than those who did (10%), which most likely reflects a difference in biology in these cases and supports a selective approach.

At the MD Anderson Cancer Center, the PV is resected and reconstructed when the vein is inseparable from the tumor and when vein resection will enable a negative margin resection. Routine PVR is not performed at our institution.

Surgical Outcomes

Despite aggressive surgical management, most patients with bile duct carcinoma will succumb to their tumors. Survival after resection of distal bile duct tumors has generally been better than that after resection of hilar CCAs. Reported 5-year survival rates range from 9% to 18% for proximal CCAs and 20% to 30% for distal lesions. Median survival is 18 to 30 months for patients without hilar involvement but only 12 to 24 months in patients with hilar involvement. Factors predictive of long-term survival after hepatic resection for CCA are T1 tumor stage, N0 lymph node status, non–mass-forming histology, and R0 resection. Vascular invasion, N2 lymph node metastases, and lobar atrophy are all associated with an adverse outcome. Lymph node metastases are found in 3% to 53% of patients; no data support extended lymphadenectomy.

The optimal palliation for patients with unresectable tumors is unclear. If the tumor has been deemed unresectable before exploration, the bile duct can be drained either percutaneously or endoscopically. The use of metallic in-dwelling stents, which are more durable than traditional stents, has made this option more appealing. Unresectable lesions at the bile duct confluence, especially Bismuth type III and IV lesions, can be particularly difficult to palliate and usually require percutaneous stenting.

Chemotherapy

No chemotherapeutic agents have been definitely shown to be effective against CCA. Single-agent trials using 5-FU have demonstrated response rates less than 15%. Other agents, such as doxorubicin, mitomycin C, and

cisplatin, used alone or in combination with 5-FU, have been no more successful.

The SWOG S0809 phase II Intergroup Trial evaluated the efficacy of postoperative capecitabine and gemcitabine followed by concurrent radiation and capecitabine in patients with extrahepatic cholangiocarcinoma and gallbladder cancer. A total of 79 patients were treated, and the combination of chemotherapy followed by chemoradiation was generally well tolerated, with grade 3 and 4 toxicities observed in 52% and 11% of patients, respectively.

An ongoing randomized multinational phase III trial (ACTICCA-1) is investigating adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after resection of cholangiocarcinoma and gallbladder cancer. The study was initiated in 2014 and will require accrual of 271 patients to assess the primary outcome of DFS.

Radiation Therapy

Several studies have investigated the role of adjuvant radiation therapy after bile duct resection. Two separate studies from The Johns Hopkins University found no benefit from adjuvant radiation therapy. Kamada et al., however, showed radiation to be beneficial in patients with surgical margins histologically positive for disease. At MD Anderson, if pathologic analysis reveals positive margins or nodes, or peritoneal invasion, patients receive a continuous infusion of 5-FU concomitantly with 54 Gy of radiation to the tumor bed. A review by Borghero et al. of 65 patients who underwent resection for extrahepatic CCA at the MD Anderson Cancer Center from 1984 to 2005 compared patients considered high risk for locoregional recurrence (R1 and/or pN1) who received adjuvant chemoradiation with either 5-FU or capecitabine (N = 42) with those at standard risk (R0pN0) treated with surgery alone. Five-year locoregional recurrence and OS were similar between groups, demonstrating that adjuvant chemoradiation may offset the locoregional recurrence risk in high-risk patients.

Radiation therapy has also been found to be effective in the palliation of unresectable bile duct cancers. Doses of 40 to 60 Gy have resulted in a median survival of 12 months, as well as reduced symptoms, probably because of improved stent patency. Palliative photodynamic bile duct therapy is also emerging as a potential palliative treatment option.

GALLBLADDER CANCER

Epidemiology and Etiology

Although carcinoma of the gallbladder is rare, it is the sixth most common cancer of the gastrointestinal tract. The tumor has been reported in all age groups, but occurs most often in patients in their 50s and 60s. There is a striking difference in incidence of the tumor between the genders: females are affected three to four times as often as males. Examination of the SEER database reveals an incidence of 1.2 cases per 100,000 people per year in the United States.

The exact etiology of carcinoma of the gallbladder is not known; however, it has been associated with several conditions. Cholelithiasis is present in 75% and 92% of gallbladder carcinoma cases. Patients with larger stones (>3 cm in diameter) have a 10 times greater risk of cancer than patients with small stones (<1 cm). In addition, gallbladder carcinoma can be found in 1% to 2% of all cholecystectomy specimens, a rate several times higher than that reported in autopsy studies. Chronic cholecystitis, including cases in which the gallbladder is calcified ("porcelain" gallbladder), is not associated with an increased risk of cancer, as was once believed.

Other factors linked to gallbladder carcinoma include cholecystoenteric fistulas, anomalous pancreaticobiliary junction, chemical carcinogens, inflammatory bowel disease, familial predisposition, chronic salmonella carrier status, and Mirizzi syndrome.

Pathologic Characteristics

Adenocarcinoma of the gallbladder is a slow-growing tumor that arises from the fundus in 60% of cases. On gross examination, the gallbladder appears firm with a thickened wall. The papillary adenocarcinoma subtype characteristically grows intraluminally and spreads intraductally. It is a less aggressive tumor that, consequently, carries a better prognosis when compared with other histologic subtypes. Adenosquamous cancer is very rare and is treated like adenocarcinoma.

Gallbladder carcinoma spreads by metastasis to the lymph nodes and direct invasion of the adjacent liver. It can spread to the peritoneal cavity after bile spillage, and cells may be implanted in biopsy tracts or at laparoscopic port sites. Lymph node metastases are found in 56% of T2 gallbladder carcinomas and peritoneal disease has been found in 79% of

patients with T4 gallbladder carcinoma. The cystic duct node, at the confluence of the cystic and hepatic ducts, is the usual initial site of regional lymphatic spread. Invasion of the liver, either by direct extension or via draining veins that empty into segments IV and V, is seen in >50% of patients. The most common site of distant extra-abdominal metastasis is the lung.

Clinical Presentation

In most series, abdominal pain is the most common presenting symptom. Nausea, vomiting, weight loss, and jaundice are other frequent symptoms. On physical examination, patients may have right upper quadrant pain with hepatomegaly or a palpable, distended gallbladder. Laboratory results are unremarkable unless the patient has developed obstructive jaundice. The tumor markers CEA and CA19-9 may be elevated in patients with gallbladder carcinoma but are neither sensitive nor specific for the disease.

Diagnosis

No laboratory or radiologic tests have shown consistent sensitivity in the diagnosis of gallbladder carcinoma. Furthermore, the paucity of clinical signs and symptoms makes preoperative diagnosis of this cancer difficult. The disease is usually diagnosed either incidentally after cholecystectomy or at an advanced stage, when presenting with a mass, jaundice, ascites, or peritoneal disease. A correct preoperative diagnosis of gallbladder carcinoma is made in fewer than 10% of cases in most series. In the Roswell Park experience, none of the 71 cases reported were diagnosed correctly preoperatively. The most common preoperative diagnoses are acute or chronic cholecystitis and malignancies of the bile duct or pancreas. Jaundice with a mid-left bile duct stricture (type 0) is almost always related to gallbladder cancer.

In the case of gallbladder carcinoma, US may demonstrate an abnormally thickened gallbladder wall or the presence of a mass. Additional imaging by contrast-enhanced CT or MRI will help determine resectability and provide information about the local extent of disease, including PV or hepatic artery invasion, lymphadenopathy, and distant metastases.

Staging

Numerous staging systems have been described for gallbladder carcinoma. The original staging system, as described by Nevin, is based on the depth of invasion and the spread of tumor. The AJCC staging system for gallbladder carcinoma was revised recently (Table 13.7). The most significant change in the AJCC staging system is that there is no longer a distinction between T3 and T4 tumors based on the depth of liver invasion; instead, T3 tumors are defined as those that directly invade the liver and/or other adjacent organs and T4 tumors as those that invade the PV, hepatic artery, or multiple adjacent extrahepatic organs or structures.

Laparoscopy has a clear role in prelaparotomy staging of gallbladder carcinoma as peritoneal disease is common with this cancer. Gallbladder carcinoma also spreads locally, metastasizing to the locoregional (N1) and distant peripancreatic/aortocaval lymph nodes (N2), often encasing the PV and hepatic artery precluding surgical resection. Two studies demonstrated that DL could prevent nontherapeutic laparotomy in 33% to 55% of patients with metastatic disease. Laparoscopy was more accurate than CT in detecting peritoneal disease in patients with locally advanced tumors, suggesting that patients with T3 and T4 lesions may benefit from DL prior to surgery.

Surgical Therapy

Standard features that make a gallbladder tumor unresectable include (a) the presence of distant hematogenous or lymphatic metastases; (b) the presence of peritoneal implants; and (c) invasion of tumor into major vascular structures such as the celiac or superior mesenteric arteries, vena cava, or aorta.

Gallbladder carcinoma in situ (Tis) and carcinoma limited to the mucosa (T1) can be treated adequately with a cholecystectomy alone, provided that the cystic duct margin is negative for disease. This approach can give 5-year survival rates as high as 100%. When carcinoma is suspected before surgery, open cholecystectomy with hepatoduodenal lymphadenectomy is advocated because the T stage cannot be accurately determined at the time of surgery and because bile spillage is a significant risk factor for peritoneal or wound recurrence.

TABLE

American Joint Commission on Cancer Staging System for Gallbladder Carcinoma, 8th edition

13.7 System for Gallbladder Carcinoma, 8th edition

Primary Tumor (T)

TX	Primary cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
Stage IVB	Any T	Any N	M1

Adapted from Edge SB. *AJCC Cancer Staging Manual.* 8th ed. New York: Springer; 2017, with permission.

The most common site of spread from gallbladder cancer is to the periportal lymph nodes (LN) and then to aortocaval LN. Celiac LN can also be involved. Long-term survival has not been demonstrated for patients who undergo resection in the setting of positive extraregional (para-aortic, celiac, or SMA) lymph nodes (N2). The most recent AHPBA/SSAT/SSO/ASCO Consensus Conference published a consensus statement recommending aortocaval LN sampling at the initiation of intended resection for gallbladder cancer. If these LN are positive on frozen section, there is no benefit to proceeding with radical resection.

Surgical treatment for T2 tumors is somewhat controversial. Because the incidence of lymph node spread in the case of T2 tumors is 56%, optimal surgical treatment for these patients would consist of at least an extended cholecystectomy that includes resection of the gallbladder en bloc along with the portal lymph nodes. A recent international review by Shindoh et al. of 252 patients with T2 gallbladder cancer found that tumors on the hepatic side (T2h) had higher rates of vascular invasion, neural invasion, and nodal metastases than tumors on the peritoneal side (T2p) of the gallbladder (P <0.001). T2h tumors were independently associated with worse survival on multivariate analysis (HR 2.7, [95% CI 1.7 to 4.2]) and higher rates of locoregional recurrence after resection.

Therefore at MD Anderson, we recommend extended cholecystectomy that includes a resection of the gallbladder en bloc along with the portal lymph nodes, and wedge or anatomical resection of the gallbladder bed (segments IVb and V) for all T2 tumors.

Locally advanced tumors (T3 and T4) often present with lymph node metastases (75% of cases) and peritoneal metastases (79%) and are often associated with long-term (>5 year) survival rates in the range of 0% to 5%. However, recent studies have reported 5-year survival rates of 21% to 44% for series of patients with T3 and T4 tumors without metastatic disease who underwent radical resection. The extent of hepatic resection is determined by the extent of tumor invasion into the gallbladder fossa and involvement of the right portal triad. To achieve a tumor-free margin, a right hepatectomy, extended right hepatectomy, or pancreaticoduodenectomy may be necessary. Pancreaticoduodenectomy is generally not warranted unless the tumor extends into the head of the pancreas. Tumors involving the hepatic artery or PV can be resected en bloc, but such an extensive procedure is not considered standard due to the associated high morbidity and mortality rates.

Multimodality Therapy

The use of single and multiple chemotherapeutic agents, either as primary or adjuvant therapy, has been disappointing. The response rate of locally advanced gallbladder cancer to 5-FU regimens is approximately 12%. 5-FU combined with doxorubicin has produced response rates of 30% to 40%. A Japanese study of adjuvant 5-FU and mitomycin C found improvement in 5-year OS among patients with gallbladder cancer who received chemotherapy (26% vs. 14%; $P = 0.037$), however this regimen has not been routinely implemented in the United States.

As mentioned previously, the SWOG S0809 phase II Intergroup Trial demonstrated safety and efficacy of postoperative capecitabine and gemcitabine followed by concurrent radiation and capecitabine in patients with extrahepatic cholangiocarcinoma and gallbladder cancer.

Radiation therapy has shown some promise in the postoperative adjuvant setting, although most series have been small. External-beam radiation therapy at a dose of 45 Gy can reduce the tumor size in 20% to 70% of cases and relieves jaundice in up to 80% of patients. At the MD Anderson Cancer Center, patients with gallbladder cancer are treated postoperatively with a combination of continuous-infusion chemotherapy with gemcitabine and cisplatin in an approach similar to that used in patients with CCA.

CONCLUSION

Many advances have been made in the surgical treatment of diseases of the liver. Advances in imaging, patient selection, and patient preparation for major hepatectomy have translated into longer and better survival of patients who undergo surgery. In particular, careful attention to liver volume measurement prior to major resection in patients with liver disease and extended resection in patients with normal liver, using such techniques as PVE, have enabled much lower morbidity and very low mortality for liver surgery. For HCC, the spectrum of treatments reflects the spectrum of the disease and/or underlying liver disease complex. Treatments range widely, including hepatic resection, OLT, tumor ablation, transarterial embolization, Y90 embolization, and external beam radiation or proton therapy. For this disease, systemic therapy has a relatively small role in a highly selected group of patients.

For patients with CRLM, criteria for resection have expanded to include

larger, multiple, and bilateral tumors. Despite these expanded indications, survival continues to improve. Furthermore, rapidly evolving effective chemotherapy is expanding the population of patients eligible for definitive surgical treatment. Understanding of specific tumor characteristics related to mutational status, such as KRAS, will likely lead to individual tailoring of both systemic and surgical treatment in the future.

These benefits from adjuvant therapy have, unfortunately, not extended to patients with biliary tract cancer. Although a small group of patients with hilar CCA and gallbladder carcinoma benefit from major hepatic resection, most patients present with unresectable disease and face limited treatment options, despite therapeutic advances in other areas.

In summary, the multidisciplinary approach to patients with liver tumors requires the involvement of specialists in hepatobiliary surgery; surgical, medical, and radiation oncology; gastroenterology; and radiology to enable optimal treatment today and advancement of multimodality treatment in the future.

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14 Pancreatic Ductal Adenocarcinoma

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EPIDEMIOLOGY

Pancreatic ductal adenocarcinoma (PDAC) is the most common invasive carcinoma of the pancreas. The disease is the third most common cause of cancer-related death in the United States, with a yearly incidence of 12.4 cases per 100,000 people. PDAC is projected to surpass colorectal cancer to become the second leading cause of cancer-related deaths in the United States by 2020. The overall risk of developing pancreatic cancer rises after age 50 years, and the median age of diagnosis is 70 years. Despite recent advances in the treatment of PDAC, the 5-year overall survival rate remains a dismal 7.7%, in part because the majority of patients present with advanced disease that precludes curative therapy. Identifying patient populations at increased risk for PDAC, enabling earlier diagnosis and application of evolving targeted therapies, is therefore imperative.

Multiple risk factors have been identified that increase the risk for development of PDAC, including genetically inherited cancer syndromes and diverse environmental factors. Inherited cancer syndromes associated with pancreatic cancer include Peutz–Jeghers syndrome (up to 132-fold risk), hereditary breast–ovarian cancer syndrome (associated with *BRCA1* or *BRCA2* mutations, up to 3.5-fold risk), familial atypical multiple mole melanoma syndrome (FAMM, up to 32-fold risk), and hereditary nonpolyposis colon cancer syndrome (HNPCC, 9-fold risk). Up to 10% of all pancreatic cancers are familial, and a person's risk of developing pancreatic cancer appears to increase with its penetrance among related family members. Identification of patient populations with genetic predispositions to PDAC may therefore improve patient outcomes through aggressive disease surveillance and early detection.

Significant risk factors for sporadic pancreatic cancer include cigarette smoking, alcoholism, and chronic pancreatitis. One case-control study of more than 1,600 patients revealed that smoking and diabetes acted

synergistically with family history to increase the risk of PDAC. Another major study revealed that diabetes mellitus and elevated insulin concentrations were associated with a twofold higher risk of PDAC. Despite the identification of several risk factors for this disease, PDAC screening in the general population is logistically and financially impractical because of its relatively low prevalence and the lack of well-defined patient subgroups at high risk for the disease.

CLINICAL PRESENTATION

The clinical presentation of pancreatic cancer is variable and nonspecific. The most common symptom at presentation is jaundice related to extrahepatic biliary obstruction, which occurs in up to 50% of all patients with PDAC, and is even more common in patients with cancers of the pancreatic head. Nonspecific complaints include constitutional symptoms, weight loss, and abdominal pain that often radiates to the back. Many patients diagnosed with pancreatic cancer have been recently diagnosed with diabetes, which may be related to β-cell dysfunction and/or peripheral insulin resistance induced by tumor-derived factors, such as adrenomedullin or islet amyloid polypeptide.

Symptoms associated with PDAC are often indicative of the stage of disease and overall prognosis. Preoperative pain, for example, is generally indicative of advanced cancer. Kelsen et al. found that patients who presented with pain had a shorter median overall survival than did patients who did not, regardless of the resectability status of their tumors. Patients may also present with physical findings that may be helpful in assessing disease stage and prognosis. Patients who present with cachexia are less likely to undergo resection and have worse survival than patients who are not cachectic at presentation. Other subtle signs of metastatic disease include enlargement of left supraclavicular lymph nodes (Virchow node) or periumbilical lymph nodes (Sister Mary Joseph node). Rectal examination may reveal a Blumer shelf, which may indicate intraperitoneal tumor deposits. Ascites, a more common finding, may indicate carcinomatosis. Rarely, patients with advanced disease present with cutaneous nodules.

DIAGNOSIS AND STAGING

The fundamental goals of the initial evaluation of a patient with a

pancreatic mass suspicious for PDAC are: (a) to secure the histopathologic diagnosis, (b) to stage the disease, and (c) to estimate the patient's physiologic profile. It is only once these fundamental goals have been met that rational treatment recommendations can be delivered.

Cross-Sectional Imaging

Computed tomography (CT) remains the most important imaging modality in the diagnostic workup of patients with suspected pancreatic cancer. CT may identify a pancreatic mass, delineate important anatomic relationships between the mass and mesenteric vasculature, and identify sites of metastatic disease.

At the MD Anderson Cancer Center (MDACC), a pancreas protocol CT scan uses water as a negative oral contrast agent and starts with precontrast imaging from the dome of the liver extending caudally to include the entire liver reconstructed to 2.5-mm slice thickness. Next, 125 mL of iodinated contrast is administered intravenously at a rate of 3 to 5 mL/s. The arterial phase uses bolus tracking and images are obtained 10 seconds after a Hounsfield unit value of 100 is reached in the aorta at the level at the celiac axis, from the dome of the liver to the iliac crests. Images for the portal venous phase are obtained at a 20-second delay from the arterial phase. Delayed images are obtained 15 seconds after the portal venous phase. The images are reconstructed to 2.5-mm slice thickness for imaging review and at 0.625- or 1.25-mm slice thickness to create coronal and sagittal reformatted images.

The primary pancreatic tumor is best seen on the arterial phase of the CT scan and typically appears as a hypodense mass against the relatively contrast-enhancing normal pancreatic parenchyma that surrounds it. Significant attention should be paid to the precise vascular anatomy and the anatomic relationships between the mesenteric vasculature and the primary pancreatic tumor. As many as 40% to 45% of patients have variants of "normal" hepatic arterial anatomy, and it is of vital importance to appreciate such variants on preoperative imaging as they directly impact operative planning. Notable examples include a replaced or accessory right hepatic artery that is present in up to 15% of patients, and most commonly arises from the SMA and courses posterior to the pancreas and posterolateral to the bile duct. An additional 2.5% of patients have a replaced common hepatic artery that arises from the SMA and follows a similar path as a replaced or accessory right hepatic artery.

The superior mesenteric vein (SMV) and portal vein (PV), as well as their major venous tributaries, are best evaluated on the portal venous phase. The initial staging CT scan has great sensitivity and specificity for determining venous involvement by tumor, and the surgeon should carefully estimate the circumferential extent of the tumor–vein interface, as well as note the vein contour and the presence or absence of deformity. Tran Cao et al. evaluated the preoperative CT scan of 254 patients who underwent pancreatoduodenectomy for PDAC and measured the tumor–vein interface as none, ≤180 degrees, >180 degrees, or associated with venous occlusion. The need for vein resection was associated with the extent of circumferential interface; for example, 34 of 38 patients (89%) with a tumor–vein interface >180 degrees or venous occlusion required a vein resection at pancreatectomy. The surgeon should also identify the location and anatomic relationships of the gastroepiploic vein, colic veins, inferior mesenteric vein (IMV), and jejunal/ileal branches of the SMV as these have variable courses and the drainage pattern directly impacts surgical options for reconstruction of the superior mesenteric–portal vein (SMV–PV) confluence, which can be expected in 40% to 60% of cases performed at high-volume centers.

Hepatic metastases are usually best visualized on the portal venous phase of CT. Liver metastases may be better characterized using magnetic resonance imaging (MRI), which is most useful as an adjunct to CT imaging. MRI should not replace a pancreas-protocol CT scan in the workup/staging of patient with suspected PDAC, although it may be a better option in patients with chronic kidney disease.

Definitions of Surgical Resectability

Over the years, the multidisciplinary team at MDACC has defined imaging criteria that characterize tumors as clinically resectable, borderline resectable, and locally advanced based on the anatomic relationship between the primary tumor and adjacent mesenteric vasculature. Several other groups and societies have offered similar definitions; a summary of various radiographic definitions of borderline resectable PDAC can be found in Table 14.1. Tumors anatomically less infiltrative than these are considered resectable, and those more infiltrative are considered locally advanced and generally unresectable.

Endoscopic Ultrasound

Endoscopic ultrasonography (EUS) may aid in diagnosis, and is particularly valuable in the evaluation of smaller pancreatic lesions: EUS has an overall sensitivity of 99% and a sensitivity of 96% for tumors <2 cm in diameter. EUS can also be used to help assess the primary tumor's relationship to the mesenteric vasculature and regional lymph node involvement.

EUS-guided fine-needle aspiration biopsy is the preferred method to secure a tissue diagnosis of the primary tumor and any suspicious regional lymph nodes. Although confirmation of the diagnosis may not always be necessary in patients with suspected PDAC who are anticipated to undergo immediate surgery, we typically recommend it to exclude other diagnoses (e.g., focal pancreatitis, lymphoma, idiopathic pancreatitis) that may masquerade as PDAC but which would be best treated nonsurgically. Further, a tissue diagnosis is required prior to the administration of chemotherapy or chemoradiation.

Serum CA 19-9

The serum tumor marker assayed most frequently in the workup of patients with suspected pancreatic cancer is carbohydrate antigen (CA) 19-9, a ganglioside Lewis blood group–associated antigen. Patients who are Lewis antigen negative (about 10% of the population) do not express CA 19-9. Although CA 19-9 is not beneficial as a screening tool, it does have value as a diagnostic tool and can also be used to monitor response to therapy. Biliary obstruction from any cause may result in an elevation in the CA 19-9 level; therefore, serum bilirubin should always be measured alongside serum CA 19-9.

The diagnostic specificity of CA 19-9 may increase in the presence of other diagnostic findings. For example, a retrospective analysis of 150 patients who underwent surgery for suspected pancreatic cancer revealed that the combination of a serum CA 19-9 level >37 U/mL, weight loss of >20 lb, and a serum bilirubin level >3 mg/dL was associated with 100% sensitivity and a 100% positive predictive value for pancreatic cancer. The CA 19-9 level should therefore always be interpreted in light of the other clinical and radiographic findings.

TABLE 14.1 Definitions of Borderline Resectable PDAC[a]

	MDACC	AHPBA/SSO/ SSAT	NCCN	Intergroup
CA	Abutment	No abutment or encasement	Contact ≤180 degrees	Interface <180 degrees
CHA	Abutment of short-segment encasement	Short-segment abutment or encasement amenable to reconstruction	Contact without extension to celiac axis or hepatic artery bifurcation amenable to resection and reconstruction	Short-segment interface of any degree amenable to reconstruction
SMA	Abutment <180 degrees	Abutment <180 degrees	Contact ≤180 degrees	Interface <180 degrees
SMV-PV	Short-segment occlusion amenable to resection and reconstruction	Abutment >180 degrees or occlusion amenable to resection and reconstruction	Contact of >180 degrees, contact of ≤180 degrees with irregularity of vein or thrombosis amenable to resection and reconstruction	Interface ≥180 degrees and/ or occlusion amenable to reconstruction

[a]Absence of extrapancreatic disease.
PDAC, pancreatic ductal adenocarcinoma; CA, celiac axis; HA, hepatic artery; CHA, common hepatic artery; SMA, superior mesenteric artery; SMV-PV, superior mesenteric vein-portal vein.

CA 19-9 may help to clinically stage PDAC and its level in the blood should influence treatment recommendations. Ferrone et al. analyzed CA 19-9 levels in a series of pancreatic cancer patients with serum bilirubin levels <2 mg/dL who underwent surgery de novo and found that preoperative CA 19-9 levels correlated with the T stage, N stage, and survival. Using the National Cancer Database, Bergquist et al. found that an elevated CA 19-9 was associated with decreased stage-specific survival, which was most dramatic in patients with early stage (I/II) cancer. Maithel et al. found that an elevation of CA 19-9 was associated with identification

of radiographically occult unresectable disease. A high-serum CA 19-9 is therefore suggestive of advanced disease irrespective of imaging findings. At MDACC, a high level of CA 19-9 would prompt the administration of preoperative systemic chemotherapy to a patient with localized PDAC, even in the absence of radiographic evidence of metastatic disease. Once treatment has been initiated, the change in CA 19-9 in response to therapy would be used as an indicator of treatment efficacy.

Staging Laparoscopy

Several studies have validated the use of staging laparoscopy to identify small hepatic and peritoneal metastases not detected by CT. Although some studies have found that laparoscopy altered the management of up to 44% of patients with radiographically resectable PDAC, the yield of laparoscopy for cancer staging has decreased as imaging techniques have improved. A 2001 study showed that laparoscopic findings enabled laparotomy to be avoided in only 4% to 13% of patients who had disease that was radiographically determined to be resectable. More recently, a large study of more than 1,000 patients revealed that laparoscopy was of even less benefit, especially among patients in whom high-quality CT had been recently performed.

At MDACC, we generally reserve laparoscopy for patients with large primary tumors, patients with cancers in the pancreatic body or tail, patients with markedly elevated CA 19-9 levels, patients with a history of severe weight loss and hypoalbuminemia, and patients with radiographic findings equivocal for the presence of metastatic disease or carcinomatosis. We may perform staging laparoscopy as a separate procedure. However, given its simplicity and low associated morbidity, staging laparoscopy often precedes planned laparotomy under the same anesthetic. We also use staging laparoscopy selectively in patients with radiographically locally advanced advanced disease (i.e., to exclude metastases prior to the administration of radiotherapy to the primary tumor and regional lymph nodes).

Biliary Drainage

Historically, it was thought that jaundiced patients were at higher risk of perioperative complications, so biliary drainage was often performed prior to pancreatectomy to improve postoperative outcomes. Several studies

have since shown that infectious complications occur more frequently in patients who undergo biliary drainage prior to surgery. In 2010, a multicenter randomized trial from the Netherlands found that the rate of serious perioperative complications was higher in patients who underwent biliary decompression with plastic biliary stents compared to those who did not undergo biliary decompression (74% vs. 39%, $P < 0.001$). A few years later, a Cochrane review confirmed that preoperative biliary drainage is associated with higher rates of serious adverse events. Thus, routine biliary drainage for patients with resectable pancreatic cancer is not routinely recommended for patients undergoing surgery de novo.

In contrast, biliary drainage of an obstructed biliary system is mandatory prior to the preoperative administration of chemotherapy or chemoradiation. In this scenario, we use short metal biliary stents to decompress the biliary tree. We have found that when compared to plastic stents, short metal stents have longer patency, require fewer ERCP sessions, and have fewer episodes of cholangitis without increasing perioperative complications. Recently, the group from the Netherlands that performed the multicenter randomized trial cited above compared a cohort of patients who underwent biliary drainage with a metal stent to the patients from the trial, who underwent biliary drainage with a plastic stent, and found that metal stents had a lower rate of PBD-related complications (24% vs. 46%, $P = 0.01$).

SURGICAL TREATMENT

Surgical Considerations

The majority of primary PDAC tumors arise in the proximal gland and are treated surgically with pancreatoduodenectomy. In contrast, distal lesions are treated with distal pancreatectomy, which typically includes splenectomy. Total pancreatectomy is generally avoided because of the high morbidity associated with the procedure and its adverse effects on pancreatic endocrine function. The surgical approach should be selected with the primary goal of achieving microscopically negative surgical margins (R0 resection).

Pancreatoduodenectomy

Patients who have a good functional status and who have a radiographic

potentially resectable primary tumor are eligible for resection. If staging laparoscopy does not reveal extrapancreatic disease, the surgeon makes either a midline or bilateral subcostal incision and carefully inspects the liver and the peritoneum for evidence of radiographically occult metastatic disease. At MDACC, we do not routinely perform intraoperative frozen-section analysis of regional lymph nodes. Instead, frozen-section analysis is made on an individual basis. For example, intraoperative frozen-section analysis of regional or extraregional lymph nodes (e.g., aortocaval nodes) may be performed in high-risk patients (patients with advanced age, significant medical comorbidities, high CA 19-9 serum levels, etc.). In such patients, the finding of metastatic disease in regional lymph nodes may suggest that pancreatoduodenectomy is unjustified, even in the absence of visceral metastases.

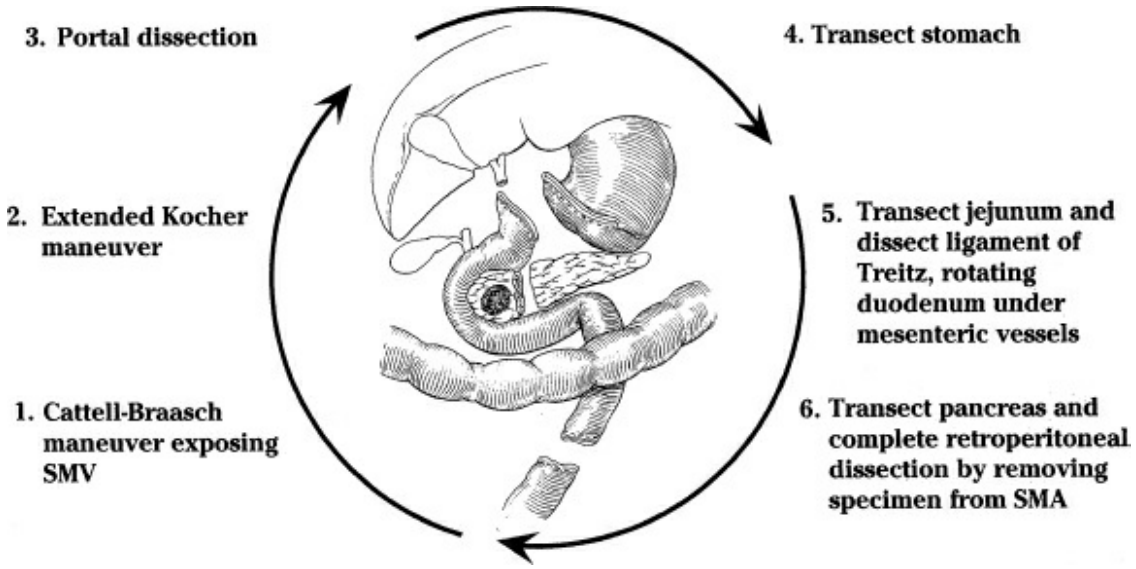

Figure 14.1 Six surgical steps of standard pancreaticoduodenectomy (clockwise resection). SMV, superior mesenteric vein; SMA, superior mesenteric artery. (From Tyler DS, Evans DB. Reoperative pancreaticoduodenectomy. *Ann Surg* 1994;219(2):211–221, reprinted with permission.)

To help organize a complex operation, minimize operative time, and provide a clear operative plan, we divide pancreatoduodenectomy into six well-defined steps (Fig. 14.1).

1. The lesser sac is entered through the avascular plane between the omentum and transverse mesocolon/colon, the right colon is mobilized, and the visceral peritoneum to the ligament of Treitz is divided, which facilitates retraction of the right colon and small

bowel. The duodenum is exposed. The infrapancreatic SMV is identified by following the course of the gastrocolic trunk or the middle colic vein to the root of the mesentery.

2. The Kocher maneuver is performed to mobilize the duodenum and head of the pancreas to the level of the left renal vein.
3. Portal dissection is performed to expose the hepatic artery both proximal and distal to the origin of the gastroduodenal artery. The gastroduodenal artery is then ligated and divided. The gallbladder is dissected from the liver, and the common hepatic duct is transected just cephalad to its junction with the cystic duct. The PV is exposed by dividing the common hepatic duct and performing cephalad retraction of the common hepatic artery; during this step, any variant hepatic artery anatomy must be identified to avoid injury.
4. If the pylorus is to be preserved, the duodenum is transected 1 to 2 cm distal to the pylorus to preserve a cuff for anastomosis. Otherwise, a standard antrectomy is performed.
5. The jejunum is transected approximately 10 cm distal to the ligament of Treitz. The jejunal and duodenal mesenteries are sequentially ligated and divided to the level of the aorta. The duodenum and jejunum are then rotated beneath the mesenteric vessels.
6. The pancreas is transected using electrocautery at the level of the PV. The specimen is separated from the SMV by ligating and dividing the small venous tributaries to the uncinate process and the pancreatic head. The SMA is completely exposed, and the lateral aspect of the vessel is skeletonized in the periadventitial plane to its origin at the aorta. This step is crucial for achieving a negative SMA margin, which is one of the main drivers of good oncologic outcome. The specimen is then removed from the abdomen.

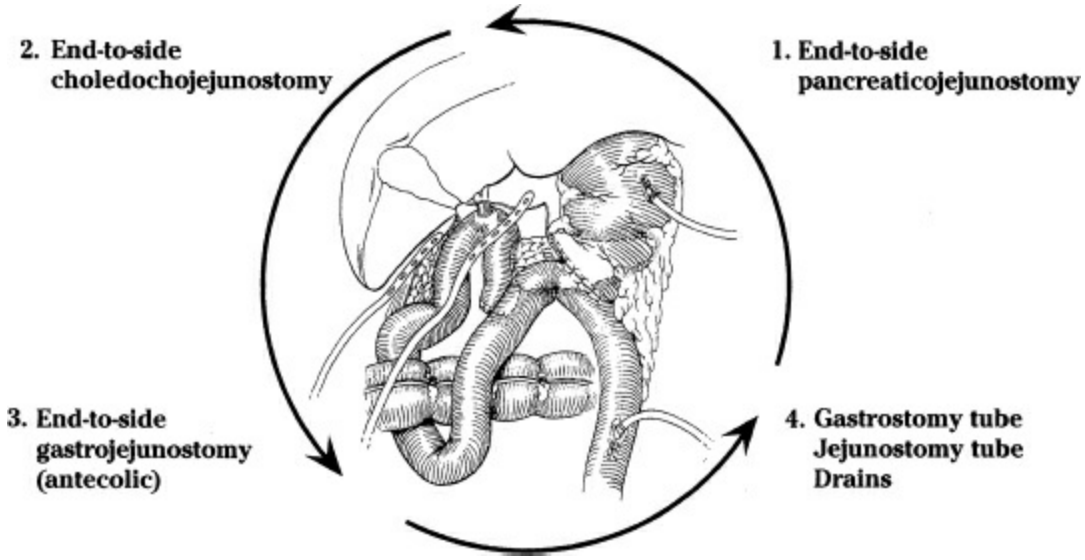

Figure 14.2 Four surgical steps of counterclockwise reconstruction following standard pancreaticoduodenectomy. (From Tyler DS, Evans DB. Reoperative pancreaticoduodenectomy. *Ann Surg* 1994;219(2):211–221, reprinted with permission.)

Reconstruction is initiated in a similar, but reverse, stepwise fashion (Fig. 14.2). The four steps of reconstruction are: (a) end-to-side pancreaticojejunostomy; (b) end-to-side hepaticojejunostomy; (c) end-to-side duodenojejunostomy or gastrojejunostomy; and (d) placement of a gastrostomy tube, a jejunostomy tube, and drains according to surgeon's preference. At MDACC, we do not routinely place a gastrostomy tube, and we reserve jejunostomy tubes for patients at high risk of nutritional deficiency following surgery.

Lymphadenectomy

PDAC commonly metastasizes through extrapancreatic lymphatics to regional lymph nodes, and lymph node involvement is a dominant prognostic factor. The primary goal of a lymphadenectomy at the time of pancreatectomy is to ensure adequate staging; although higher lymph node counts have been correlated with better outcomes, it has been difficult to prove that extensive lymphadenectomy significantly impacts survival given PDAC's high rate of early systemic dissemination.

Lymphadenectomy at the time of pancreatectomy is guided by vascular and visceral anatomy. The regional nodal basins that are included in a standard pancreatoduodenectomy are located along the bile duct, common

hepatic artery, PV, pancreatoduodenal arterial arcades, SMV, and along the lateral wall of the SMA. Studies have evaluated the role of extended lymphadenectomy and have failed to demonstrate a survival benefit compared to a less extensive, “standard” lymphadenectomy. This high-level data notwithstanding, at MDACC, the standard lymphadenectomy performed with pancreatoduodenectomy includes lymph nodes (numerical stations): anterior and posterior to the common hepatic artery (8a/p), along the proper hepatic artery (12a1/2), common bile duct and hepatic duct (12b1/2), PV (12p1/2), gallbladder (12c), posterior superior and posterior inferior pancreatic head (13a/b), superior mesenteric artery (14a/b), and anterior superior and anterior inferior pancreatic head (17a/b), while a distal pancreatectomy and splenectomy includes lymph node stations in the splenic hilum (10), along the splenic artery (11p/d) and superior margin of the pancreas (18).

Mesenteric Vascular Resection

Vascular involvement by cancer, particularly involvement of the SMV–PV, does not represent an absolute contraindication to pancreatectomy. We have found that resecting and reconstructing the SMV–PV confluence and the major first order venous branches at pancreatoduodenectomy is both safe and associated with an overall survival rate similar to that of patients who do not require venous resection to achieve negative surgical margins. At MDACC, most patients with tumors that appear on cross-sectional imaging to involve the SMV or PV receive preoperative chemotherapy and/or chemoradiation. Venous resection should be performed only to achieve a negative resection margin and not as part of an en bloc regional pancreatectomy.

Cross-sectional imaging can predict the need for vascular resection. On the other hand, evidence for histologic vein invasion is not needed to justify a venous resection; pancreatitis and/or tumor- or treatment-related fibrosis may mandate venous resection, even though true invasion of the vessel may not exist. In the series by Tran Cao et al., 98 of 254 patients with resectable or borderline resectable PDAC underwent venous resection, among whom only 69% had histopathologic evidence for vein invasion.

The strategy used for venous reconstruction should be dictated by the patient’s venous anatomy and the location and extent of venous involvement. The surgical objective is to preserve portal venous flow from

the stomach, spleen, and intestines while minimizing the risk of sinistral portal hypertension.

Unlike venous resection and reconstruction, arterial resection is generally unjustified during pancreatoduodenectomy. A notable exception is when the tumor appears to extend along the gastroduodenal artery to involve the proper or common hepatic artery, or when a replaced right hepatic artery or replaced common hepatic artery arising from the SMA appears to be involved by tumor. In such cases, we usually offer patients an extended course of preoperative therapy before considering tumor resection.

ADJUVANT (POSTOPERATIVE) THERAPY FOR RESECTED PDAC

The first study of adjuvant chemoradiation in patients with resected pancreatic cancer was performed by the Gastrointestinal Study Group and reported in 1985. The patients who received postoperative 5-FU–based chemoradiation had significantly longer median overall survival (21.0 months) than patients who underwent surgery alone (10.9 months), thus establishing 5-FU as the standard for postoperative chemoradiation. However, subsequent trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the European Study Group for Pancreatic Cancer (ESPAC) did not confirm that there was a survival advantage associated with adjuvant chemoradiation. Indeed, the ESPAC-1 trial suggested that chemoradiation was actually harmful. The Radiation Therapy Oncology Group study 0848 is ongoing and is randomizing patients to adjuvant gemcitabine or gemcitabine plus radiotherapy. This study should help clarify the role of adjuvant chemoradiation therapy in patients with resected pancreatic cancer.

In 2008, the Charite Onkologie and the Radiation Therapy Oncology Group evaluated the role of adjuvant gemcitabine for resected pancreatic cancer. The CONKO trial determined that adjuvant gemcitabine was associated with an increased disease-free and overall survival (22.8 vs. 20.2 months, $P = 0.005$) relative to surgery alone. The ESPAC-3 trial compared adjuvant gemcitabine to infusional 5-FU and found similar median survival (23.6 vs. 23.0 months), but noted that gemcitabine had fewer treatment-related serious adverse events (7.5% vs. 14%, $P < 0.001$). The most recent randomized trial, ESPAC-4, randomized patients with resected pancreatic cancer to receive either adjuvant gemcitabine and

capecitabine or gemcitabine monotherapy. The median survival was longer for patients treated with gemcitabine and capecitabine than gemcitabine alone (28.0 vs. 25.5 months, $P = 0.03$), and there was no significant difference in adverse events between the two groups. To date, the evidence indicates that adjuvant chemotherapy improves survival, and that the combination of gemcitabine and capecitabine appears to be the most effective. Based on the existing evidence, the American Society of Clinical Oncology (ASCO) recommends that all patients with resected pancreatic cancer who did not receive preoperative therapy be offered 6 months of adjuvant therapy, initiated within 8 weeks of surgical resection.

PREOPERATIVE (NEOADJUVANT) THERAPY

Resectable Tumors

The argument for administering preoperative therapy to patients with resectable pancreatic cancer begins with the fact that 80% to 90% of patients who undergo potentially curative resection develop recurrence. Additionally, up to 50% of patients who undergo surgery for resectable pancreatic cancer ultimately do not receive postoperative adjuvant therapy for reasons related to the surgery (i.e., complications or nutritional impairment) and/or the disease itself (i.e., disease progression). Administering preoperative therapy enables patients to receive requisite "adjuvant" therapy immediately and ensures that all patients who undergo resection receive systemic therapy. Preoperative therapy also facilitates the selection of patients for surgery who are most likely to benefit from it; patients with clinically occult but progressive systemic disease can often be identified during the preoperative therapy period and spared the potential morbidity associated with pancreatic resection.

To date, there are no published phase III randomized trials that have compared neoadjuvant systemic chemotherapy to adjuvant chemotherapy for resectable pancreatic cancer, but there are some phase I/II studies that demonstrate the safety of preoperative systemic chemotherapy and suggest its therapeutic impact. In 2007, Palmer et al. reported a phase II randomized trial comparing two regimens of neoadjuvant chemotherapy (gemcitabine vs. gemcitabine/cisplatin). Both regimens were well tolerated and 54% of patients underwent resection after completion of neoadjuvant chemotherapy. The R0 resection rate was 75% following neoadjuvant chemotherapy, compared to 51% for a contemporary population of patients

at the same institution who were treated with surgery alone. The median survival for those who underwent surgical resection was 28.4 months. In 2008, Henirich et al. performed a phase II trial that evaluated neoadjuvant chemotherapy with the combination of gemcitabine and cisplatin. Twenty-four of 28 patients on the trial underwent surgical resection. The chemotherapy resulted in a decrease in the level of CA 19-9, and a grade I, II, III, and IV pathologic response was seen in 46%, 54%, 0%, and 0%, respectively. The rate of postsurgical complication rates was not different from historical patients, and the median survival for the 24 patients who underwent surgical resection was 26.5 months. Recently, Ielpo et al. published a phase II trial of neoadjuvant gemcitabine plus nab-paclitaxel in 25 patients with resectable and borderline resectable pancreatic cancer. Nine of the 17 patients who underwent surgical resection had resectable tumors at diagnosis—all 9 had an R0 resection and 7 of 9 had a major pathologic response. Phase III randomized trails comparing neoadjuvant chemotherapy to surgical resection are needed to further clarify the role of neoadjuvant chemotherapy for patients with resectable PDAC. One such trial awaiting publication is the NEOPAC study, a randomized multicenter phase III trial comparing neoadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine to adjuvant gemcitabine alone in patients with resectable PDAC.

MDACC has a long-standing history of administering neoadjuvant chemoradiation for resectable PDAC. Evans et al. conducted a phase II trial of preoperative gemcitabine-based chemoradiation (30 Gy); 24% of patients had disease progression prior to surgical resection. However, the R0 resection rate among patients who underwent pancreatoduodenectomy was >90% and the median survival for the entire cohort and for those who completed all planned therapy were 23 and 34 months, respectively. In a phase II trial performed by Turrini et al., patients received 5-FU and cisplatin along with 45 Gy of radiation prior to surgery. Disease progression was noted in 39% of patients prior to surgical resection. A complete pathologic response was seen in 13% of patients who underwent resection, and an R0 resection was achieved in 92% of patients. Two recent randomized trials by Golcher et al. and Casadei et al. were designed to compare preoperative chemoradiation and surgery to surgery alone, but both trials closed early due to slow accrual. These studies did redemonstrate that chemoradiation is feasible and safe prior to surgical resection. Although concerns have been raised about the safety of

pancreatic surgery following chemoradiation, we recently reviewed a contemporary cohort of patients with PDAC that underwent pancreatectomy either de novo or following preoperative chemoradiation and found that chemoradiation did not increase the 90-day morbidity or mortality rate.

Currently, there are several ongoing phase I/II studies evaluating the role of immunologic agents and kinase inhibitors in combination with chemoradiation, as well as some studies that are investigating the role of new radiotherapy modalities (intensity-modulated radiation therapy [IMRT] and stereotactic body radiation therapy) in patients with resectable pancreatic cancer. The NEOPA trial is a phase III study that is randomizing patients to gemcitabine-based neoadjuvant chemoradiation (50.4 Gy) versus surgery alone, which will hopefully more clearly define the role of neoadjuvant chemoradiation in patients with resectable pancreatic cancer.

Borderline Resectable Tumors

MDACC has defined and developed multidisciplinary treatment strategies for patients with borderline resectable (BR) pancreatic cancer (Table 14.1). In 2008, Katz et al. proposed a definition for BR pancreatic cancer based upon strict anatomic imaging criteria, but also included other clinical factors. Patients were classified as BR-A, BR-B, or BR-C, where A refers to tumor "anatomy," B stands for cancer "biology," and C refers to the patient's "condition" or performance status. BR-A tumors meet specific anatomic imaging criteria (Table 14.1). BR-B tumors have associated clinical findings suspicious for extrapancreatic disease such as indeterminate liver lesions, serum carbohydrate antigen (CA) 19-9 ≥1,000 U/mL in the setting a normal bilirubin, or biopsy-proven metastasis to regional lymph nodes. BR-C patients are advanced in age (≥80 years old) or have severe comorbidities requiring extensive evaluation or optimization, or depressed performance status (ECOG ≥2). In a series of 160 patients with BR cancers using this scheme who were treated with preoperative chemotherapy and/or chemoradiation, 41% of patients underwent resection. The resection rate for patients with BR-A, BR-B, and BR-C disease was 38%, 50%, and 38%, respectively. The median overall survival for the entire cohort was 18 months with a 5-year survival of 18%. For the 66 patients who completed all therapies, the median survival was 40 months with a 5-year survival of 36%. These prospective data provided

support for further trials investigating this multidisciplinary approach.

Although consensus statements advocate the administration of both systemic chemotherapy and chemoradiation to patients with borderline resectable PDAC, most of the data used to support this approach are based on data from retrospective, single institution studies. The Alliance Trial A021101, conducted by Katz et al. was a prospective, multicenter, trial of this approach. Twenty-two patients initiated therapy, which consisted of modified FOLFIRINOX (4 cycles) and chemoradiation (50.4-Gy external beam radiation and capecitabine) prior to pancreatectomy. Fifteen of 22 (68%) patients underwent resection; 12 (80%) required vascular resection, 14 (93%) had microscopically negative margins, and 5 (33%) had less than 5% residual cancer cells. Following the success of this trial, a phase II trial (Alliance A021501) was designed to randomize patients with BR pancreatic cancer to modified FOLFIRINOX (8 cycles), surgery and adjuvant FOLFOX (4 cycles), or modified FOLFIRINOX (7 cycles), short course radiation therapy, surgery, and adjuvant FOLFOX (4 cycles). This trial and others should more clearly define the optimal treatment strategy for patients with BR PDAC.

SURGICAL OUTCOMES

In 2006, Winter et al. reported the Johns Hopkins experience of 1,423 pancreatoduodenectomies for pancreatic cancer from 1970 to 2006. The perioperative mortality rates in the 1970s, 1980s, 1990s, and 2000s were 30%, 5%, 2%, and 1%, respectively. Forty-two percent of patients had a margin positive resection. The median survival durations in the 1970s, 1980s, 1990s, and 2000s were 8, 14, 17, and 19 months, respectively. The 5-year survival rates for the 1970s, 1980s, 1990s, and 2000s also improved over time—5%, 11%, 18%, and 20%, respectively. Of note, the median and 5-year survival rates for the 1990s and 2000s were not significantly different, suggesting that the maximum impact of surgery on survival had been realized.

In 2009, Katz et al. published the cumulative MDACC experience of the surgical treatment of patients with localized pancreatic cancer. Three hundred twenty-nine patients treated between 1990 and 2002 were evaluated. Two hundred fifty-three (77%) patients received preoperative chemotherapy and/or chemoradiation. Most patients (92%) underwent pancreatoduodenectomy. A total of 108 (33%) patients underwent vascular resection and reconstruction. Regional lymph node metastases were

identified in 157 (48%) of patients and margins were microscopically positive in 52 (16%) patients. The median and 5-year overall survival was 23.9 months and 27%, respectively. Recently, a more inclusive 25-year MDACC experience of preoperative therapy and pancreatoduodenectomy was published, which included 622 patients. Over that time period, a larger proportion of patients who underwent resection had borderline resectable and locally advanced tumors. The use of induction systemic chemotherapy and postoperative adjuvant chemotherapy increased over time. R0 resection and vascular resection rates increased over time, and were 94% and 66%, respectively, in the most recent time period. Over the 25-year time period, the median overall survival increased from 24 to 43 months, and the 5-year overall survival increased from 23% to 35%. These results are a testament to the evolution of multidisciplinary care in the setting of advances in chemotherapeutic regimens, selection of surgical patients, and the optimization of surgical therapy. Further improvements in patient outcomes will come from improved systemic therapy and treatment sequencing.

POSTOPERATIVE ONCOLOGIC SURVEILLANCE

There is little evidence to guide the frequency or intensity of surveillance strategies after potentially curative resection for PDAC. Tzeng et al. performed a cost-effectiveness analysis comparing no follow-up to 3- or 6-month intervals with or without CA 19-9 testing and routine CT scans. A clinical evaluation every 6 months with CA 19-9 testing and no imaging seemed to be the most cost effective strategy and provided a similar survival benefit when compared to more frequent and intense surveillance strategies. ASCO recommends that patients who have completed treatment of potentially curable pancreatic cancer be offered follow-up visits at 3- to 6-month intervals, admitting that there is little evidence to support this recommendation. Nonetheless, we typically see patients every 6 months for the first 2 years following potentially curative resection with a CT scan of the abdomen, chest x-ray, and CA 19-9 level. Visits are spread out to yearly after 5 years.

LOCALLY ADVANCED TUMORS

Chemotherapy

The ACCORD-11/PRODIGE-4 trial, a phase III randomized trial, compared FOLFIRINOX to gemcitabine in patients with metastatic pancreatic cancer, and found that FOLFIRINOX had a higher response rate with increased progression-free and overall survival. Based upon the efficacy of FOLFIRINOX in patients with metastatic disease, it seemed rational to also use it for patients with locally advanced (LA) pancreatic cancer. Marthey et al. reported a prospective cohort study conducted at multiple institutions in France that administered FOLFIRINOX to patients with locally advanced pancreatic cancer. Grade III–IV toxicities occurred in 26% of patients, but only five patients had to stop therapy due to toxicities. According to RECIST criteria, disease progression, stable disease, and partial response were seen in 16%, 56%, and 16% of patients, respectively. Seventy-five percent of patients underwent consolidation therapy, and an R0 resection was achieved in 25 of 28 patients who underwent surgical resection. The median progression-free and overall survivals for the entire cohort were 13 and 22 months, respectively leading to the conclusion that surgery may also be applied selectively following chemotherapy in patients with locally advanced disease. In 2015, Ferrone et al. presented a retrospective series of patients with pancreatic cancer (BR and LA) treated with neoadjuvant FOLFIRINOX +/– chemoradiation, many of whom had preoperative imaging that met radiographic criteria of unresectability, but were able to undergo R0 resection (92%).

Chemoradiation

LAP07 was an international phase III trial that randomized patients with LA PDAC to chemotherapy or chemoradiotherapy, if there was no evidence of disease progression after 4 months of gemcitabine with or without erlotinib. After 4 months of chemotherapy (gemcitabine +/– erlotinib), 269 of 442 patients had no evidence of disease progression and were randomized to chemoradiotherapy or 2 more months of the same chemotherapy. Three-dimensional conformal radiation therapy was used with a total planned dose of 54 Gy in 30 fractions over 6 weeks with concurrent capecitabine. There was no difference in progression-free survival (9.9 vs. 8.4 months) – or overall survival (15.2 vs. 16.5 months), between patients treated with chemoradiation or chemotherapy, respectively. Locoregional progression occurred less frequently in the chemoradiation group (32%) than in the chemotherapy group (46%), whereas distant progression occurred more often in patients treated with

chemoradiation than chemotherapy (60% vs. 44%).

High-dose radiation therapy may also have a role in the treatment of patients with advanced disease. Krishnan et al. reported a series of 200 consecutive MDACC patients with locally advanced PDAC who received induction chemotherapy (gemcitabine or FOLFIRINOX) for a median of 3.5 months followed by chemoradiation. Forty-seven patients with unresectable tumors >1 cm from the closest GI mucosa were treated with dose-escalated IMRT that delivered a biologically effective dose (BED) >70 Gy. The patients who received a BED >70 Gy had improved local–regional recurrence free survival and overall survival when compared to those who received a BED ≤70 Gy.

Ablative Therapies

Over the years, several ablative therapies have been investigated for the treatment of locally advanced pancreatic cancer. Radiofrequency and microwave ablation use thermal damage to destroy the cancer cells, but can also damage vital structures in the surrounding area like the bile duct or mesenteric vessels and have reported morbidities rates of 28% to 40% and mortality rates of 7.5%.

Irreversible electroporation (IRE) has gained increasing interest in recent years. IRE uses two electrodes to deliver electrical pulses that disrupt the cell wall lipid bilayer leading to apoptosis, but does not affect the structure of the extracellular matrix. In 2015, Paiella et al., reported a prospective safety and feasibility study in patients with locally advanced PDAC. That same year, Martin et al. reported a series of 200 patients with locally advanced pancreatic cancer that were treated with IRE alone (N = 150) or in combination with surgical resection (N = 50). Fifty-four of the 150 patients who underwent IRE alone suffered a complication—32% of the complications were at least grade III in severity. The median overall survival following IRE alone was 18 months. The PANFIRE study was a phase I/II study designed to evaluate the safety and efficacy of percutaneous CT-guided IRE for locally advanced pancreatic cancer, which found a 40% rate of grade III/IV complications. It is clear that ablative therapy for LA PDAC is associated with a significant risk of severe complications, and as of yet has not been proven to be more efficacious than systemic chemotherapy or consolidative strategies, such as high-dose chemoradiation.

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15 Pancreatic Neuroendocrine Tumors and Multiple Endocrine Neoplasia

Jordan M. Cloyd and Jeffrey E. Lee

SPORADIC PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of neoplasms that arise from pancreatic islet cells and account for 1% to 3% of pancreatic malignancies. PNETs may be classified as functional or nonfunctional, depending on their ability to secrete hormones and elicit characteristic symptoms (Table 15.1). PNETs exhibit a wide range of biologic aggressiveness, from benign and indolent to malignant and aggressive. Although the American Joint Committee on Cancer (AJCC) uses the same TNM staging system for PNETs as for pancreatic adenocarcinoma, PNETs are more commonly classified according to a proliferation-based grading system (Table 15.2) which influences diagnostic modalities, treatment decisions, and prognosis. PNETs comprise approximately 7% of all neuroendocrine tumors, and the incidence appears to be increasing, presumably at least in part because of the increased use of high-quality cross-sectional imaging. Fortunately, there have been significant advances in diagnostic imaging, tumor localization, and therapeutic options in recent years.

Nonfunctional Pancreatic Neuroendocrine Tumors

Sixty to 90% of PNETs are nonfunctional (NF-PNETs), and they occur most commonly in the pancreatic head. NF-PNETs are often diagnosed late in the course of the disease because symptoms do not become evident until the primary tumor grows large enough to compress adjacent structures or large-volume metastatic disease develops. Patients with NF-PNETs usually present with abdominal pain, weight loss, obstructive jaundice, bleeding, and/or intestinal obstructive symptoms. Increasingly, NF-PNETs are identified incidentally on cross-sectional imaging performed for other indications. The vast majority of metastases occur in

the liver; other less common sites include bone, peritoneum, adrenal glands, and spleen. The median overall survival (OS) duration among all patients with NF-PNETs is approximately 3.2 years: 7.1 years in patients with resectable disease, 5.2 years in patients with locally advanced and unresectable disease, and 2.1 years in patients with unresectable metastatic disease.

Diagnosis

NF-PNETs are usually diagnosed with computed tomography (CT) or magnetic resonance imaging (MRI), where they characteristically appear as well-circumscribed hyperenhancing lesions on contrast-enhanced scans. Hypoenhancement, cystic changes, and calcifications can also be seen. Imaging features may overlap with other entities including pancreatic adenocarcinoma and benign processes. Endoscopic ultrasound (EUS) may assist in confirming the diagnosis via fine-needle aspiration, evaluating the relationship with critical vessels, and defining the extent and distribution of the multiple PNETs often associated with patients who have inherited endocrine tumor syndromes. Somatostatin receptor scintigraphy (octreotide imaging) may be used selectively to help identify occult metastases, particularly in regional lymph nodes or the liver. In general, well-differentiated PNETs are positive on octreotide imaging and negative on positron emission tomography, with the opposite being true for poorly differentiated tumors.

NF-PNETs may secrete a variety of hormones whose effects are often not clinically apparent. For example, as many as 75% of patients with NF-PNETs have elevated fasting pancreatic polypeptide levels, whereas chromogranin A levels are elevated in 60% to 100% of patients. However, it is important to remember that chromogranin A levels may be elevated in patients even in the absence of a PNET, due to advanced age, heavy alcohol use, inflammatory conditions, renal failure, or chronic proton pump inhibitor (PPI) use. Neuroendocrine markers may occasionally be helpful in surveillance and in monitoring response to treatment; they are less helpful in establishing a diagnosis of NF-PNET. In contrast, a prebiopsy-elevated CA19-9 and/or carcinoembryonic antigen (CEA) level in a patient with a hypodense pancreatic tumor and normal bilirubin level suggests that the tumor represents an adenocarcinoma rather than a PNET.

TABLE

15.1 Functional Pancreatic Neuroendocrine Tumors

Pancreatic Endocrine Tumor	% of PNETs	Malignant (%)	Pancreatic Cell Type	Clinical Manifestation	Diagnostic Test
Insulinoma	40–60	<10	Beta	Hypoglycemia with symptom relief after glucose administration	• Monitored 72-hour fast • Insulin, proinsulin, C-peptide
Gastrinoma	20–50	60–90	Delta	Peptic ulcer disease	• Fasting gastrin (off PPI) • Basal to maximal acid output ratio • Basal acid output >15 mEq/hr • Nocturnal (12 hours) gastric acid secretion test • Secretin stimulation test
VIPoma	Rare	40–70	A–D	Watery diarrhea, hypokalemia, achlorhydria, dehydration	Fasting VIP
Glucagonoma	Rare	50–80	Alpha	Diabetes, necrolytic migratory erythema, weight loss, depression, psychosis, venous thrombosis	Fasting glucagon
Somatostatinoma	Rare	>70	Delta	Mild diabetes, cholelithiasis, steatorrhea, weight loss, anemia, diarrhea	Fasting somatostatin

TABLE 15.2 WHO 2010/ENETS Grading System

Grade	Differentiation	Ki-67 Index (%)	Mitoses/10 High-Power Fields
Low	Well	≤2	<2
Intermediate	Well	3–20	2–20
High	Poor	>20	>20

Treatment

Surgical resection with regional lymph node dissection is generally recommended for patients with localized, sporadic NF-PNETs, particularly if the tumor is >1 to 2 cm in diameter, growing, or causing symptoms, and if the patient is relatively young with a good performance status. There is growing consensus that very small (i.e., 1 cm) PNETs identified incidentally that are not associated with nodal metastasis or other symptoms can safely be monitored without immediate surgery in many patients, particularly in older adults and in those with significant comorbidities. Modestly sized PNETs (1 to 2 cm) without radiographic or clinical evidence of involved regional lymph nodes may be selectively considered for primary resection without lymph node dissection. The anatomic considerations for determining the resectability of, and the surgical approach to, patients with sporadic NF-PNETs are generally the same as those for pancreatic adenocarcinomas (see Chapter 14, Pancreatic

demonstrate local invasiveness, limited resections (e.g., central pancreatectomy, spleen-preserving distal pancreatectomy, enucleation) and minimally invasive resection (e.g., laparoscopic surgery) can be selectively applied to patients with PNETs when appropriate. In contrast, since patients with locally advanced NF-PNETs (e.g., surrounding the celiac axis or superior mesenteric artery) often have relatively favorable survival duration, incomplete resection or primary tumor debulking is not recommended because of the potential morbidity associated with palliative pancreatic resection and the absence of demonstrable survival or palliative benefit to incomplete resection of a primary PNET. However, resection of a primary PNET with concomitant or staged resection of oligometastatic disease (e.g., liver metastases) can be indicated in selected patients at low risk. There is no standard adjuvant systemic therapy for patients who undergo potentially curative surgical resection. Long-term follow-up after surgery is essential since up to 50% of patients who undergo complete resection develop metachronous liver metastasis, for which surgery and/or systemic therapy can be indicated.

Functioning Pancreatic Neuroendocrine Tumors

Insulinoma

In 1935, Whipple and Frantz first described the clinical manifestations of insulinoma as a triad of hypoglycemic symptoms while fasting, blood glucose levels <50 mg/dL, and symptomatic relief after glucose administration (Whipple triad). Insulinomas are the most common type of functioning PNET. Approximately 10% exhibit malignant behavior, 10% are associated with MEN1, and 10% are multiple. Importantly, most patients with malignant insulinomas present with distant metastasis rather than develop metastases metachronously. Insulinomas oversecrete insulin, and the resultant hypoglycemic episodes are exacerbated during periods of fasting or exercise. During an insulin surge, patients may develop a sympathetic overdrive characterized by sweating, weakness, tremors, hyperphasia, and palpitations. Neuroglycopenic symptoms including confusion, visual changes, altered consciousness, and convulsions may also occur.

Diagnosis

The most reliable test for diagnosing insulinomas is a monitored 72-hour fast, during which the patient’s plasma glucose, C-peptide, proinsulin, and

fast, during which the patient's plasma glucose, C-peptide, proinsulin, and insulin levels are measured every 4 to 6 hours. The test is continued until the plasma glucose level is <45 mg/dL and the patient develops hypoglycemic symptoms. It is helpful to remember that 33% of patients become symptomatic within 12 hours, 80% within 24 hours, 90% within 48 hours, and 100% within 72 hours. The diagnosis of insulinoma is established by a serum insulin concentration ≥6 μU/mL (50% of patients with an insulinoma will have an insulin level >24 μU/mL), an insulin-to-glucose ratio >0.3, a C-peptide level ≥0.2 nmol/L, a proinsulin level ≥5 pmol/L, and an absence of plasma sulfonylurea. An insulin level >7 μU/mL after a prolonged fast in the presence of a blood sugar <40 mg/dL is highly suggestive of an insulinoma, and virtually all patients with an insulinoma have an insulin-to-glucose ratio of >0.3. Patients who self-administer exogenous forms of insulin usually have low C-peptide and proinsulin levels because commercial insulin does not contain insulin precursor or cleavage fragments. Patients who surreptitiously consume oral hypoglycemic agents may be identified by the presence of plasma sulfonylurea.

Depending on the size of the tumors, insulinomas may be visualized by CT, MRI, or EUS. Octreotide imaging is of limited use because many insulinomas do not express somatostatin receptors. Although rarely necessary in the current era because of improvements in cross-sectional imaging and EUS, selective intra-arterial calcium injection of major pancreatic arteries with hepatic venous sampling (calcium arterial stimulation test) has been reported to successfully regionalize tumors in more than 80% of patients with insulinomas. A twofold increase in insulin after intra-arterial calcium infusion (0.025 mEq/kg) identifies the arterial distribution supplying the tumor.

Treatment

The primary treatment for sporadic insulinoma is surgical resection. Before surgery, glucose levels should be controlled with frequent small meals and diazoxide, a drug that inhibits insulin release and promotes glycogenolysis. During surgery, intraoperative ultrasound is encouraged in order to localize small tumors deep in the pancreatic parenchyma, locate the main pancreatic duct (important if enucleation is planned), and exclude the presence of parenchymal liver metastases. Enucleation is appropriate for many smaller insulinomas, whereas larger lesions will require formal

intervention, the surgeon may consider pancreatic biopsy to rule out beta cell hyperplasia or adult nesidioblastosis; however, blind distal pancreatectomy is no longer recommended when a tumor cannot be localized. Instead, the surgeon should abandon attempts at resection and repeat biochemical testing, imaging, and possibly regionalization studies. Most patients with insulinoma are cured after resection; local recurrence, even after enucleation, is rare; and the median disease-free survival after resection of malignant insulinoma is approximately 5 years.

Gastrinoma

In 1955, Zollinger and Ellison first described the clinical trial of atypical peptic ulcerations, gastric hypersecretion with hyperacidity, and a non–insulin-producing islet tumor of the pancreas. Gastrinomas secrete gastrin, a hormone that induces hyperchlorhydria and parietal cell hyperplasia. Patients with sporadic gastrinoma (a very rare condition) often present at about 45 years of age with abdominal pain (75% to 100%), diarrhea (35% to 73%), heartburn (44% to 64%), duodenal and prepyloric ulcers (71% to 91%), and complications of peptic ulcer disease (PUD). Gastrinomas account for <1% of all cases of PUD. Approximately 75% of gastrinomas are sporadic; the remaining 25% are associated with MEN1. Most gastrinomas are located in the duodenum and the pancreas (3:1 ratio), but primary gastrinoma tumors have been identified in other sites including the stomach, jejunum, peripancreatic tissue, ovaries, and liver. The majority of gastrinomas are malignant, and the most important predictor of survival is the presence of liver metastases.

Diagnosis

Patients with a suspected gastrinoma should be evaluated with a fasting gastrin level and gastric pH at 1 to 2 weeks after discontinuation of PPIs. Withdrawing PPIs in patients with suspected gastrinoma should be done carefully because perforation can occur if the patient is not closely monitored. A fasting gastrin level >1,000 pg/mL with a gastric pH of <2.5 is highly suggestive of gastrinoma. Other causes of hypergastrinemia include PPI use, vagotomy, fundectomy, gastric outlet obstruction, resection of the large bowel, chronic renal failure, and autoimmune or *Helicobacter pylori* gastritis with atrophy and associated achlorhydria.

The majority of patients with gastrinomas have a basal–maximal acid output ratio ≥0.6, or a 12-hour nocturnal gastric acid secretion >100 mEq.

output ratio ≥0.6, or a 12-hour nocturnal gastric acid secretion >100 mEq. To establish the diagnosis in the setting of occult disease, a basal acid output of 15 mEq/hr and a positive secretin stimulation test have traditionally been used, although such testing is now rarely employed. The secretin stimulation test involves administering 2 units/kg of intravenous secretin after an overnight fast. Serum gastrin levels are obtained at 15 and 2 minutes before secretin injection and again at 0, 2, 5, 10, and 20 minutes after infusion. The test is positive for gastrinoma when there is a paradoxical increase in serum gastrin by more than 200 pg/mL over baseline levels. Importantly, secondary neuroendocrine tumors, referred to as "type I gastric carcinoids" and pathologically indistinguishable from gastrinomas, occur in patients with achlorhydria due to atrophic gastritis, apparently due to the relentless stimulation of the very high gastrin levels in such patients. The gastrinomas in such patients are indolent, typically presenting as multiple small (<1 cm) tumors in the gastric fundus, and should almost always be treated conservatively, for example, with endoscopic monitoring and excision.

Once a biochemical diagnosis of gastrinoma has been established, tumor localization studies are performed: CT and MRI are beneficial in localizing larger tumors, whereas esophagogastroduodenoscopy with EUS is necessary to identify smaller tumors. CT and MRI are the most sensitive imaging modalities for identifying liver metastases from gastrinoma, which are likely only in patients with primary tumors ≥2 cm in diameter. Although historically 80% to 100% of gastrinomas have been detectable by a combination of selective abdominal angiography and selective arterial secretin injection, this invasive imaging strategy is now rarely necessary.

Treatment

Before surgery, acid hypersecretion must be controlled, typically with twice-daily dosing of full-dose PPI. Because resection has been shown to increase OS in patients with sporadic gastrinoma, surgical treatment has been recommended even if a tumor cannot be identified on preoperative localization studies. If a tumor is identified on imaging, then resection along with regional lymph node dissection is recommended. At least 30% to 50% of gastrinoma patients have regional lymph node metastasis at the time of operative intervention.

For nonlocalizable gastrinomas, surgical exploration should include the following: exploration of the lesser sac to evaluate the pancreatic body and

to inspect the pancreatic head; duodenotomy with digital palpation to identify small duodenal wall tumors; periduodenal, peripancreatic head, portal, and hepatic arterial lymph node dissection; and exploration of extrapancreatic locations including the ovary, stomach wall, small bowel, omentum, and intestinal mesentery. Intraoperative endoscopy with transillumination may help localize duodenal wall tumors; if done, it should be performed before duodenotomy. Total gastrectomy may be considered for patients in whom medical therapy has failed, who are noncompliant, or who have recurrent complications from PUD. Indications for total gastrectomy in the modern era should be rare.

Vasoactive Intestinal Polypeptidoma

Vasoactive intestinal polypeptide (VIP)-secreting tumors (VIPomas) are also referred to as Verner–Morrison syndrome or watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome. These are very rare PNETs characterized by large-volume secretory diarrhea, electrolyte imbalances (hypokalemia and hypercalcemia), dehydration, hypochlorhydria or achlorhydria, hyperglycemia, and flushing. At presentation, 60% to 80% of VIPomas are metastatic. The 5-year OS rate for patients with VIPomas (all stages) is 69%. The 5-year survival rate is 60% for patients with metastatic disease and 94% for patients without metastasis. More than 80% of VIPomas are isolated to the pancreas while 75% involve the pancreatic body and tail. Extrapancreatic primary tumors that secrete VIP have been identified in the chest and retroperitoneum and have included such tumors as ganglioneuroblastomas, ganglioneuromas, and neuroblastomas.

Diagnosis

A fasting plasma VIP level >500 pg/mL along with high-volume diarrhea is suggestive of a VIPoma. Concomitant elevation of serum pancreatic polypeptide helps to confirm the diagnosis. These tumors are usually identified on CT, MRI, EUS, or octreotide scans as part of an evaluation for diarrhea. Other options for tumor localization, rarely necessary in the current era, include mesenteric arteriography and portal venous sampling.

Treatment

VIPomas are usually treated with surgical resection and regional lymph node dissection. Before operative intervention, patients should be

node dissection. Before operative intervention, patients should be hydrated, their electrolytes should be normalized, and they should receive octreotide to control the diarrhea.

Glucagonoma

Glucagonomas arise from the alpha cells of the pancreas and are characterized by excess glucagon secretion that results in glucose intolerance (occurring in >90% of patients), weight loss, neuropsychiatric disturbances (e.g., depression or psychosis), and venous thrombosis. Approximately 70% of glucagonoma patients develop necrolytic migratory erythema, a rash that occurs on the lower abdomen, perineum, perioral area, and/or feet. The majority of glucagonomas arise in the body or tail of the pancreas, are malignant, and frequently present with metastasis. The characteristic patient with a glucagonoma is elderly, ill, and has a large pancreatic tail mass.

Diagnosis

An inappropriately elevated fasting glucagon level >500 to 1,000 pg/mL is diagnostic of a glucagonoma. However, elevated glucagon levels may occur in patients with cirrhosis, pancreatitis, diabetes mellitus, prolonged fasting, renal failure, burns, sepsis, familial glucagonemia, and acromegaly. A diagnosis of glucagonoma can be confirmed with a biopsy of the area of necrolytic migratory erythema. Glucagonomas are most often easily identified with CT and/or MRI because they are usually >5 cm in diameter.

Treatment

Management of localized glucagonomas includes surgical resection and regional lymph node dissection. Metastatic disease should be resected when possible to alleviate symptoms. Necrolytic migratory erythema secondary to unresectable glucagonoma can usually be effectively treated with somatostatin.

Somatostatinoma

Somatostatinomas, which arise from the delta cells of the pancreas, are extremely rare and have an estimated incidence of 1 in 40 million. To date, only about 200 cases of somatostatinomas have been reported. Ninety percent of somatostatinomas are malignant. Although the majority (90%)

disorders such as neurofibromatosis type 1 (NF1), MEN1, and von Hippel–Lindau (VHL) disease.

Somatostatinomas are most frequently located in the pancreas or duodenum; however, there have been reports of somatostatinomas occurring in other locations such as the jejunum. Patients with duodenal somatostatinomas commonly present with symptoms of obstruction, whereas patients with pancreatic somatostatinomas frequently present with diabetes mellitus, cholelithiasis, steatorrhea, weight loss, anemia, and/or diarrhea. Five-year OS rates for patients with somatostatinoma are 100% for patients with localized disease and 60% for patients with distant metastatic disease.

Diagnosis

Because of their rarity and nonspecific symptoms, patients with somatostatinomas are often diagnosed late in the course of the disease. A somatostatin level >100 pg/mL and a tumor identified on CT, MRI, octreotide scan, and/or EUS suggest a diagnosis of somatostatinoma. Pancreatic somatostatinomas are typically solitary, large, and located in the head of the pancreas. Duodenal somatostatinomas, which are generally smaller than pancreatic somatostatinomas, can be identified with esophagogastroduodenoscopy.

Treatment

Somatostatinoma patients frequently present with metastatic disease; nevertheless, these patients should undergo surgical resection when possible. Given the high incidence of cholelithiasis in somatostatinoma patients, cholecystectomy should be performed at the time of surgery. As for other functional PNETs, tumor debulking of metastatic disease may be selectively considered for palliation.

Management of Liver Metastases

All patients with liver metastases from PNETs should be considered for surgical resection. Although associated with high recurrence rates, surgical resection of neuroendocrine metastases is associated with improved progression-free survival (PFS). A recent meta-analysis of almost 1,500 gastroenteropancreatic neuroendocrine tumors found a 5-year OS rate of 70.5% in patients who underwent liver resection. Predictors of poor outcomes in this series included extrahepatic disease, incomplete resection,

outcomes in this series included extrahepatic disease, incomplete resection, and poor histologic grade.

When patients are not candidates for surgical resection of liver metastases, alternative therapies should be considered. Microwave or radiofrequency ablation, transarterial chemoembolization, and yttrium-90 radioembolization are helpful strategies that may improve local control and palliate symptoms, although there is insufficient evidence to recommend one strategy over another. Finally, although reasonable outcomes have been described in well-selected patients with metastatic neuroendocrine carcinoma who underwent liver transplantation, worse results have been observed in patients with tumors of pancreatic origin; therefore, transplantation is typically not recommended.

Systemic Therapy

Significant advancements in treatment options have been seen in recent years for patients with unresectable and/or metastatic disease. The goal of systemic therapy in these settings is to prolong survival and improve quality of life by controlling symptoms. The mainstay of treatment is somatostatin analogs, given the common presence of somatostatin receptors on PNETs. The PROMID and CLARINET double-blind randomized controlled trials demonstrated significant improvements in PFS in patients with enteropancreatic neuroendocrine neoplasms who received long-acting release octreotide. Increasingly, PNETs are being treated with targeted therapies. As an example, the RADIANT-3 trial demonstrated improved PFS in patients with NF-PNETs who received the mTOR inhibitor everolimus. Similar results have been shown with the VEGF inhibitor sunitinib. Traditional cytotoxic chemotherapy is typically reserved for patients with high-grade tumors, since most well-differentiated tumors are indolent and response rates are lower. Streptozocin was one of the first systemic agents to demonstrate activity in the setting of metastatic PNETs; a combination of streptozocin, doxorubicin, and fluorouracil has frequently been used at MD Anderson. More recent research has focused on the use of oral temozolomide with or without capecitabine, given its ease of administration and favorable side-effect profile.

MULTIPLE ENDOCRINE NEOPLASIA AND OTHER

PANCREATIC NEUROENDOCRINE TUMORS

Even though the majority of PNETs are sporadic, several hereditary syndromes are associated with an increased incidence of PNETs. Although surgical resection is generally indicated, as is the case for sporadic PNETs, a unique aspect of PNETs in the setting of an inherited tumor syndrome is their multiplicity. Therefore, surgical treatment of patients with inherited PNETs may be influenced by the need to preserve pancreatic parenchyma and avoid the long-term sequela of pancreatectomy (i.e., diabetes), particularly when the identified tumors are relatively small and distributed throughout the pancreas.

Multiple Endocrine Neoplasia Type 1

MEN1, also known as Wermer syndrome, is an autosomal dominant disorder caused by germline mutations in the *MEN1* gene. Located on chromosome 11q13, *MEN1* is a tumor suppressor gene that encodes menin, a protein involved in DNA replication, repair, transcription, and chromatin modification. Individuals with MEN1 most commonly develop tumors in the anterior pituitary gland, parathyroid glands, and endocrine pancreas. More than 20 other endocrine tumors (e.g., foregut carcinoids and adrenocortical and medullary lesions) and nonendocrine tumors (e.g., facial angiofibromas and collagenomas) have been described in MEN1. Thyroid nodules, meningiomas, ependymomas, leiomyomas, and lipomas are also associated with MEN1.

Parathyroid Tumors in MEN1

The most common first clinical manifestation associated with MEN1, primary hyperparathyroidism (PHPT), is also the most common endocrinopathy overall. The age of onset for PHPT ranges from 20 to 25 years, which is approximately 30 years earlier than that for sporadic PHPT. Nearly all MEN1 patients develop multiglandular PHPT by the age of 50 years. Therefore, all patients younger than 40 years who are diagnosed with multiglandular PHPT should be considered for genetic counseling and/or testing. Patients with PHPT may be completely asymptomatic or they may develop nephrolithiasis, osteoporosis, myopathy, fatigue, PUD, and/or neurocognitive deficits such as depression and difficulty sleeping.

Two major operative strategies for MEN1 patients with PHPT include

Two major operative strategies for MEN1 patients with PHPT include subtotal parathyroidectomy and total parathyroidectomy. Because MEN1 patients are at increased risk of thymic carcinoid and because supernumerary parathyroid glands are often located in the thymus, cervical thymectomy is recommended as a component of both strategies. At MD Anderson, we prefer subtotal parathyroidectomy (3.5-gland resection) with cervical thymectomy and parathyroid cryopreservation as the initial operation. In the event of recurrent hyperparathyroidism, which occurs in 30% to 40% of patients who undergo subtotal parathyroidectomy, we recommend performing completion (total) parathyroidectomy with autografting and cryopreservation of the remaining parathyroid tissue. We avoid total parathyroidectomy as the initial approach because as many as one-third of patients treated in this way develop permanent postoperative hypoparathyroidism.

Pituitary Tumors in MEN1

More commonly identified in women, anterior pituitary adenomas are diagnosed in 10% to 60% of MEN1 patients at an average age of 35 years (the same age as seen in sporadic tumors). Pituitary adenomas are the first clinical manifestation of MEN1 in approximately 10% of patients. The most common pituitary adenomas are prolactinomas (60%), nonfunctioning pituitary tumors (15%), somatotropinomas (10% to 15%), and corticotropin-secreting tumors (5%). Up to 85% of MEN1-associated pituitary tumors are macroadenomas that often present with symptoms of local compression such as headache, visual field deficits, hypopituitarism, temporal lobe epilepsy, mild hyperprolactinemia from stalk compression, and cranial nerve III or VI dysfunction. Pituitary adenomas are best detected by MRI with and without gadolinium at 3-mm intervals.

Women with prolactinomas may present with amenorrhea and/or galactorrhea, whereas men with prolactinomas may present with sexual dysfunction and/or gynecomastia. A serum prolactin level >200 ng/mL and an associated adenoma on MRI confirm the diagnosis of prolactinoma. Patients with an adenoma on MRI and who have an elevated prolactin level <100 ng/mL most likely have a nonfunctional tumor leading to mildly elevated prolactin from stalk compression. The treatment of prolactinomas begins with long-acting dopamine agonists such as cabergoline or bromocriptine, although patients with MEN1-associated prolactinomas generally have a poorer response to treatment. Surgical

Somatotropinomas produce excess insulin-like growth factor 1 (IGF-1) and/or growth hormone, leading to gigantism in prepubescent children and acromegaly in adults. The diagnosis is rendered with an elevated IGF-1 and a tumor on MRI; serum growth hormone levels may or may not be elevated. Inability to suppress growth hormone levels to <5 ng/dL after administering 1.75 g/kg (max 100 g) of oral glucose is diagnostic of a somatotropinoma. Corticotropin-secreting pituitary tumors lead to the development of Cushing disease. The clinical manifestations of corticotropin-secreting tumors include central weight gain, mood changes, thinning of the skin, easy bruising, diabetes, hypertension, and osteoporosis. Excess cortisol production can be detected by measuring the urinary free cortisol level. The diagnosis may also be confirmed by obtaining a plasma adrenocorticotrophic hormone level or a midnight salivary cortisol level, or by performing the dexamethasone suppression test. Inferior petrosal sinus sampling is the most invasive but also the most definitive test. The treatment of choice for both somatotropinomas and Cushing disease is surgical resection.

Pancreatic Neuroendocrine Tumors in MEN1

PNETs develop in 50% to 75% of patients with MEN1, and metastatic PNETs are the most frequent cause of death among MEN1 patients. PNETs associated with MEN1 are usually diagnosed at an earlier age than in sporadic cases. PNETs may be solitary or multifocal, functional or nonfunctional (>50%), and solid or cystic. Microscopically, the pancreas in MEN1 patients demonstrates multiple microadenomas, islet cell hypertrophy, hyperplasia, and dysplasia. Tumor localization strategies in patients with MEN1-associated PNETs are the same as in patients with sporadic PNETs. In general, early diagnosis and surgical excision of MEN1-associated PNETs is associated with improved OS.

Timing of surgical intervention in MEN1 patients with NF-PNETs must still be individualized. Due to the frequent multiplicity of tumors, the relatively rare presence of liver metastases in patients with small primary PNETs, and the desire to maintain insulin production by preserving islet cell mass, surgery is often delayed in MEN1 patients until the largest tumor is ≥2 cm in size. When surgery is performed, an attempt is usually made to resect all identified pancreatic tumors; for example, enucleation of a superficial pancreatic head tumor is sometimes combined with formal distal pancreatectomy. Splenic preservation is a reasonable goal in most

distal pancreatectomy. Splenic preservation is a reasonable goal in most patients with moderately sized distal pancreatic tumors, and minimally invasive distal pancreatectomy is appropriate in selected patients.

Although several types of functional PNETs can occur within the same patient, one hormonal syndrome usually dominates. Gastrinoma, which has been identified in as many as 60% of MEN1 patients, is the most common functional pancreaticoduodenal endocrine tumor in MEN1 patients. More than 80% of MEN1-associated gastrinomas are located in the duodenum. Duodenal gastrinomas are usually very small tumors that are often not readily apparent on standard imaging modalities or upper endoscopy. Therefore, in MEN1 patients with an elevated gastrin level and a radiographically evident PNET, it should not be assumed that their PNET is the source of the elevated gastrin level. Furthermore, patients with MEN1-associated hypergastrinemia and concomitant PHPT should usually undergo parathyroidectomy first because achieving normocalcemia may decrease serum gastrin levels.

The surgical management of gastrinoma in MEN1 patients is controversial. Unlike gastrinomas in patients with sporadic Zollinger–Ellison syndrome (ZES), MEN1-associated gastrinomas are significantly more likely to recur, and long-term cure is less likely after surgical resection. Therefore, current recommendations include surgical exploration for gastrinoma only in patients with biochemically confirmed ZES and a radiographically apparent primary tumor that is ≥2.0 cm or with apparent gastrinoma lymph node spread. Management of ZES in patients without an identifiable tumor consists of medical control of acid hypersecretion, although a regional operation (duodenotomy and regional lymph node dissection) can be selectively considered as part of the comprehensive surgical treatment of an MEN1 patient with hypergastrinemia in whom open distal pancreatectomy is planned for treatment of PNETs.

MEN1-associated insulinomas, which are diagnosed in 10% to 20% of patients with MEN1, are often multifocal, present earlier than sporadic insulinomas, and may be located throughout the pancreas. Although 85% to 95% of MEN1-associated insulinomas are benign, they have a higher recurrence rate after surgical resection than do sporadic insulinomas. As many as 5% of MEN1 patients with PNETs have other functioning tumors such as glucagonomas, VIPomas, or somatostatinomas. The diagnosis and treatment of these rare tumors are similar to that of their sporadic

Screening of MEN1 Patients

Given the high penetrance of the previously mentioned disorders, patients with positive genetic testing or those at high risk of MEN1 should undergo regular screening. Screening for pituitary tumors begins with annual serum prolactin and IGF-1 levels as early 5 years of age. Brain MRI every 2 to 3 years may also be considered. Screening for PHPT may begin as early as 8 years of age and involves annual serum calcium and parathyroid hormone (PTH) levels. An elevated serum calcium level with an inappropriately elevated PTH level confirms the diagnosis of PHPT. Finally, screening for functional PNETs includes annual serum fasting glucose, insulin, gastrin, chromogranin-A, glucagon, and proinsulin, whereas surveillance for NF-PNETs requires CT or MRI of the abdomen every 1 to 3 years. Patients with new, growing, or intermediate-size tumors (2 to 3 cm) in whom surgery is not immediately planned may require more frequent imaging (e.g., every 6 months).

Diagnosis of MEN1 and the Role of Genetic Testing

Obtaining a thorough and accurate family history is key to identifying MEN1 patients. Patients are clinically diagnosed with MEN1 if they develop two or more of the classic MEN1-associated tumors—pituitary, parathyroid, or endocrine tumors of the pancreas or duodenum—or have one of the classic tumors and at least one close relative with a clinical diagnosis of MEN1. Genetic counseling and the option of genetic testing should be offered to all patients with a clinical diagnosis of MEN1, to patients with one classic feature and a nonclassic tumor such as a foregut carcinoid or lipoma, and to patients with one of the classic tumors plus a family history of a classic tumor.

As many as 90% of MEN1 patients have an identifiable *MEN1* mutation although multiple mutations have been identified within the *MEN1* gene, and specific mutations may be unique to each family. Early genetic testing for MEN1 has many potential advantages: facilitating early identification and treatment of disease, preventing complications associated with long-term hormonal excess, allowing for consideration of preimplantation or prenatal genetic testing to assist in family planning, and/or allowing mutation-negative relatives to be spared unnecessary clinical screening.

Multiple Endocrine Neoplasia Type 2

MEN2 is an autosomal dominant disorder characterized by the

Multiple Endocrine Neoplasia Type 2

MEN2 is an autosomal dominant disorder characterized by the development of medullary thyroid carcinoma (MTC), pheochromocytomas, and PHPT. MEN2 is divided into three different subtypes: MEN2A, familial MTC, and MEN2B. About 95% of MEN2 patients have germline activating missense mutations of the *RET* proto-oncogene. The *RET* gene encodes a tyrosine kinase receptor that is expressed in neuroendocrine and neural cells and consists of 21 exons located on chromosome 10q11.2. The specific RET mutation in MEN2 patients can be used to predict the MEN2 subtype as well as the aggressiveness of MTC. MTC is usually the first manifestation of MEN2, and the age of presentation ranges from the first to fourth decade of life.

MEN2A

MEN2A, the most common subtype of MEN2, is associated with the MTC in 90% of patients, PHPT in 20% to 30%, and pheochromocytoma in up to 50% of patients. *RET* mutations are identified in more than 95% of MEN2A patients. Patients who test negative for a *RET* mutation may be diagnosed with MEN2A if at least two of the classic features of the disease (i.e., MTC, pheochromocytoma, and PHPT) are present. Recently, familial MTC has been classified as a clinical variant of MEN2A, in which MTC is the only manifestation. Even though these patients are at low risk of developing pheochromocytoma and PHPT, families once thought to have familial MTC have later developed clinical manifestations of MEN2A and therefore must be monitored for the development of these tumors.

MEN2B

Less common than MEN2A, MEN2B is a condition characterized by MTC (nearly 100%), a marfanoid habitus, medullated corneal nerve fibers, ganglioneuromatosis, and pheochromocytoma (50% of patients). Patients with MEN2B typically develop MTC approximately 10 years earlier than do patients with MEN2A. MEN2B patients commonly have an elongated face with enlarged, nodular lips; thickened and everted eyelids; and neuromas of the tongue and oral mucosa. Patients may also develop skeletal abnormalities such as genu valgum, pes cavus, club foot, and kyphoscoliosis. Neuromas are frequently identified in the gastrointestinal tract but may also occur in organs with a submucosa, such as the bronchi and bladder. In addition, abdominal distention, megacolon, constipation,

Medullary Thyroid Carcinoma in MEN2

MTC develops from the parafollicular cells (C cells) of the thyroid gland that produce calcitonin, a hormone that decreases plasma calcium levels by inhibiting osteoclastic bone absorption and stimulating urinary excretion of calcium and phosphate. In MEN2 patients, MTC is preceded by the development of C-cell hyperplasia, leading to an increase in serum calcitonin levels. Because the majority of C cells are located in the superior one-third of the thyroid gland, MTC is most commonly concentrated in this location. MTC in patients with MEN2 is usually bilateral and multicentric. A serum calcitonin level >1,000 pg/mL and an elevated CEA level suggest MTC. A positive pentagastrin stimulation test and the identification of a thyroid mass with positive cytologic evidence of MTC on ultrasonography-guided fine-needle aspiration biopsy render the definitive diagnosis.

MTC is a relatively aggressive disease. Patients may present with neck pain, a palpable neck mass, or diarrhea due to elevated serum calcitonin levels. Patients who have dysphagia and/or hoarseness probably have advanced disease. Metastasis first develops in cervical or mediastinal lymph nodes, followed by the lungs, liver, and bones. Surgical resection is the treatment of choice for MTC. The timing and extent of surgery should be individualized according to the patient's specific *RET* mutation to achieve the best overall outcome (Table 15.3). The disease is generally resistant to chemotherapy, and radioactive iodine is ineffective. Targeted therapies, with tyrosine kinase inhibitors (TKIs) such as vandetanib and cabozantinib are associated with improved PFS in patients with advanced MTC, but are associated with significant toxicity and therefore usually reserved for patients with large tumor burden and documented disease progression.

The initial evaluation of patients diagnosed with MTC includes performing cervical neck ultrasonography and measuring serum CEA, calcium, and calcitonin levels. Before operative intervention, serum PTH, and plasma metanephrines and/or normetanephrines should be measured to rule out pheochromocytoma and PHPT. If a pheochromocytoma is present, it should be resected before thyroidectomy to prevent a hypertensive crisis. Total thyroidectomy with prophylactic central neck dissection is recommended for patients with no evidence of local invasion or lymph node metastasis. In patients who have calcitonin levels >400 pg/mL or evidence of lymph node metastasis, a three-phase CT of the neck, chest,

recommended for patients with no evidence of local invasion or lymph node metastasis. In patients who have calcitonin levels >400 pg/mL or evidence of lymph node metastasis, a three-phase CT of the neck, chest, and liver is necessary to rule out distant metastasis. Patients who demonstrate lateral cervical lymph node metastasis should undergo a lateral neck dissection of levels IIA, III, IV, and V on the affected side. In patients with established distant metastatic disease, limited surgical resection to preserve speech and swallowing may be considered.

Thyroid hormone suppression therapy is not effective for patients with MTC, so patients should receive only thyroid hormone replacement therapy after total thyroidectomy. Baseline serum calcitonin and CEA levels should be measured 2 to 3 months after operative intervention and every 6 to 12 months thereafter. Cervical ultrasonography should be performed 6 months after surgical resection. The detection of calcitonin after total thyroidectomy indicates that residual or persistent disease is present. Patients in whom serum calcitonin and CEA levels are undetectable may be monitored with biochemical assessments alone.

Primary Hyperparathyroidism in MEN2A

PHPT occurs in 10% to 35% of patients with MEN2A. Although the diagnosis and the clinical presentation of PHPT in MEN2A are similar to those seen in sporadic or MEN1-associated cases, surgical intervention for MEN2A-associated PHPT differs in several important ways. MEN2A patients who have PHPT at the time of initial thyroidectomy should undergo resection of visibly enlarged parathyroid glands with possible forearm autograft, subtotal parathyroidectomy (leaving one or a piece of one gland in situ), or total parathyroidectomy with forearm autograft. In patients who develop PHPT after initial thyroidectomy, surgical intervention should be guided by the identification of abnormal parathyroid glands on preoperative imaging, and the use of forearm autografting should be considered. During thyroidectomy for patients with MEN2A, especially those with a strong family history of PHPT, normal devascularized parathyroid glands should be implanted into the forearm.

TABLE **15.3** Aggressiveness of MTC Based on *RET* Mutation

American Thyroid Association Level	RET Mutation	Aggressiveness of MTC	Timing of Prophylactic Thyroidectomy
A	768, 790, 791, 804, 891	Lowest risk of aggressiveness (lower serum calcitonin, lower tumor stage, and higher rate of cure than level B tumors)	May be delayed beyond 5 years of age if serum *calcitonin* and neck ultrasound are normal[a]
B	609, 611, 618, 620, 630	Lower risk of aggressiveness	Consider prophylactic thyroidectomy before age 5 years (may be delayed beyond 5 years of age if serum calcitonin and neck ultrasound are normal[a])
C	634	High risk of aggressiveness	Before 5 years of age
D	883, 918	Highest risk of aggressiveness and youngest age at onset	Within the first year of life

[a]Must be screened with annual serum calcitonin levels and cervical ultrasonography; if abnormal, thyroidectomy is indicated at that time.
MTC, medullary thyroid carcinoma; RET, rearranged during transfection.

Pheochromocytoma in MEN2

Pheochromocytomas—catecholamine-secreting tumors of the adrenal medulla—develop in up to 50% of MEN2A patients during their lifespan and typically 10 to 20 years earlier than in patients with sporadic pheochromocytoma. Patients with pheochromocytomas typically present with headache, sweating, palpitations, hypertension, and anxiety. Pheochromocytomas may be unilateral or bilateral as well as synchronous or metachronous. Elevated plasma-free metanephrines and normetanephrines or urinary metanephrines are necessary for the diagnosis. Once biochemical diagnosis is established, CT or MRI of the abdomen should be performed to identify an adrenal tumor. Metaiodobenzylguanidine (MIBG) scanning may be used for localization in difficult cases.

The treatment of choice for pheochromocytomas is surgical resection. At least 1 to 2 weeks before surgery, patients should be well hydrated and treated with an alpha antagonist. The recommended initial dose of

phenoxybenzamine is 10 mg twice a day with a goal to achieve a blood pressure of 130/80 mm Hg while sitting and 100 mm Hg systolic when standing. When needed, beta blockers may be used to obtain a target heart rate of 60 to 70 beats per minute while sitting and 70 to 80 beats per minute while standing. Beta-1 blockers (atenolol 12.5 to 25 mg three times per day, or metoprolol at 25 to 50 mg two to three times per day) are preferred and must always be used with alpha-adrenergic blockade. Beta blockers should never be used alone or before the initiation of alpha blockade, due to the risk of exacerbating hypertension in these patients.

The most common operative approach in patients with a unilateral pheochromocytoma is minimally invasive adrenalectomy. At MD Anderson, we prefer retroperitoneoscopic adrenalectomy over a transperitoneal laparoscopic approach for patients with modestly sized, clinically benign pheochromocytomas. This approach avoids the need for intra-abdominal solid-organ mobilization and for repositioning in patients with bilateral tumors. If possible, cortical sparing adrenalectomy should be performed in MEN2 patients with bilateral pheochromocytomas because the procedure can prevent postoperative corticosteroid dependence in up to 65% of patients. Otherwise, patients who undergo bilateral adrenalectomy will require lifelong corticosteroid supplementation. With careful preoperative planning and meticulous surgical technique, including minimizing unnecessary dissection to preserve remnant blood supply, cortical-sparing adrenalectomy can be performed successfully with use of minimally invasive techniques, including via a retroperitoneoscopic approach.

Diagnosis of MEN2 and the Role of Genetic Testing

Genetic counseling and testing is recommended for patients who are diagnosed with MTC, primary C-cell hyperplasia, cutaneous lichen amyloidosis, or early-age-of-onset pheochromocytoma. *RET* genetic testing should also be suggested to patients who have a positive family history of MEN2 or FMTC. Patients at risk of developing MEN2A should begin genetic testing before 5 years of age, and patients at risk of MEN2B should be tested shortly after birth. If possible, all first-degree relatives should be offered genetic testing before the age of recommended prophylactic thyroidectomy when a specific *RET* mutation is identified within a family.

von Hippel–Lindau Disease

VHL is an autosomal dominant disease characterized by mutations of the *VHL* gene, and is associated with pancreatic pathology in 20% to 75% of patients. VHL patients most commonly develop pancreatic cysts, but 10% to 17% will develop PNETs. Other characteristics of this disease include hemangioblastomas of the nervous system, retinal angiomas, clear cell renal carcinomas, pheochromocytomas, and endolymphatic sac tumors. PNETs associated with VHL are usually solitary but may be multiple, can be located anywhere in the pancreas, and are typically diagnosed at an earlier age than in sporadic PNETs. PNETs associated with VHL may be more indolent than PNETs associated with MEN1. Liver metastasis can occur but is uncommon in tumors <3 cm. When evaluating cystic lesions in patients with VHL, it is important to keep in mind that benign pancreatic cysts are much more common than cystic PNETs.

Tuberous Sclerosis

Tuberous sclerosis is a rare, autosomal dominant disorder associated with mutations in the *TSC1* gene on the 9q34 chromosome or the *TSC2* gene on the 16p13.3 chromosome. Tuberin, a *TSC2* gene product associated with cell growth and proliferation, has been associated with the development of malignant PNETs in tuberous sclerosis patients.

von Recklinghausen Disease

Associated with a mutation of the *NF1* tumor suppressor gene, von Recklinghausen disease, also known as NF1, is manifested by the development of neurofibromas, café-au-lait macules, optic gliomas, Lisch nodules, bony lesions, short stature, learning disabilities, and macroencephaly. Malignant pheochromocytomas are the most common endocrine malignancy associated with NF1; however, a few case reports of pancreatic insulinomas and duodenal somatostatinomas have been published.

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16 Adrenal Tumors

Casey B. Duncan and Jeffrey E. Lee

INTRODUCTION

Proper surgical evaluation and treatment of adrenal tumors can be complex and includes the application of appropriate diagnostic imaging, selective endocrine hormone evaluation, and when indicated either minimally invasive or open surgery. Advances in diagnostic imaging have facilitated early detection and accurate surgical treatment planning, whereas advances in minimally invasive and open surgical techniques have improved the surgeon's ability to minimize surgical morbidity while maximizing outcomes.

Evaluation of the patient presenting with an adrenal mass requires an understanding of relevant adrenal endocrine physiology. Appropriate biochemical evaluation and radiographic assessment of an identified adrenal mass are crucial prior to any surgical intervention, as biochemical evaluation helps determine the functional status of the tumor and informs management, including the potential role for surgery. Common functioning adrenal tumors include cortisol-producing adrenal adenomas, pheochromocytomas, aldosteronomas, and adrenal cortical carcinomas. Nonfunctioning adrenal tumors include nonfunctioning adrenal adenomas or "incidentalomas," metastases to the adrenal gland, and uncommon primary tumors including angiomyelolipomas. Newer developments in genetics, especially for patients with pheochromocytomas, are being increasingly incorporated into the management of patients with adrenal tumors and their families.

ANATOMY

The adrenal glands are paired, pyramid-shaped structures located in the retroperitoneum atop the superior–medial aspect of each kidney. The normal adult adrenal gland weighs approximately 4 to 5 g, with

dimensions spanning approximately 4 to 5 cm vertically, 3 cm transversely, and 1 cm in the anteroposterior plane. The adrenal glands are soft and highly vascular structures. The adrenal glands have two discrete embryologic, anatomic, and functional layers: the cortex (outer) and the medulla (inner). The cortex is normally a thin (1 to 2 mm), bright yellow layer which produces steroid hormones. From superficial to deep, it is subdivided into the zona glomerulosa which produces the mineralocorticoid aldosterone, the zona fasciculata which produces the glucocorticoid cortisol, and the zona reticularis which produces the sex steroids, primarily androgens. The medulla is a dark red-gray layer which produces norepinephrine and epinephrine.

The arterial blood supply to the adrenal glands is derived from branches of the inferior phrenic artery, the renal artery, and contributions directly from the aorta. Nutrient arteries coalesce and form a capsular arterial plexus that sends capillaries throughout the cortex, which subsequently combine to form a venous portal system that drains into the adrenal medulla. In the medulla, the vessels come together to join the central adrenal vein. The adrenal medulla is also supplied by arteriae medullae that penetrate directly into the medullary substance. Although there are some small veins draining the surface of the adrenal cortex, the central vein drains most of the blood from the medulla stemming from the cortex via the capsular plexus. The right adrenal vein is short and wide as it exits the gland and immediately enters the posterolateral aspect of the inferior vena cava at an acute angle. The left adrenal vein exits anteriorly and usually drains into the left renal vein, although it occasionally may enter the inferior vena cava directly. It is therefore typically easier to obtain vascular control of the left adrenal vein. Vascular control and cannulation of the right adrenal vein can be challenging, in particular with increasing size of the adrenal tumor (Fig. 16.1).

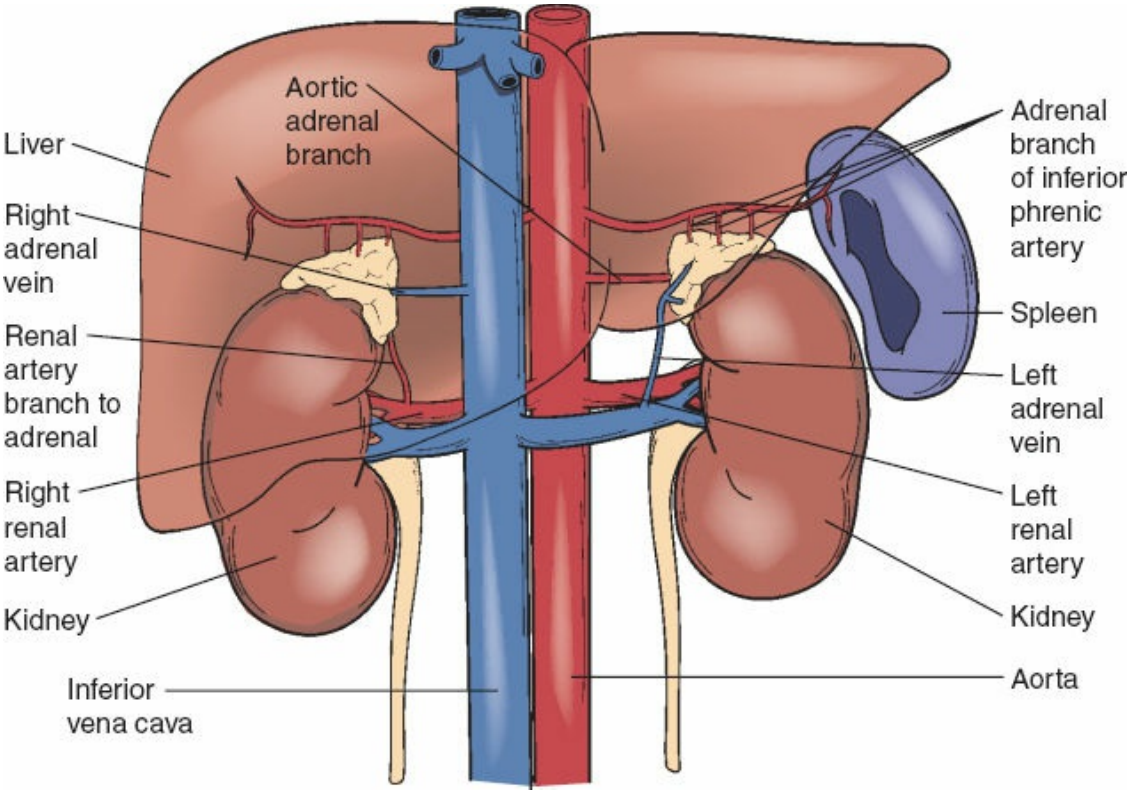

Figure 16.1 Adrenal vascular anatomy. (Reprinted with permission from Kawamura D, Nolan T. *Abdomen and Superficial Structures, 4th ed*. Philadelphia, PA: Wolters Kluwer, 2017.)

ALDOSTERONOMA

Introduction

Primary aldosteronism was first described by J. W. Conn in 1955 in the setting of a 4-cm aldosterone secreting adenoma in association with hypertension and hypokalemia (Conn syndrome). Since then, it has been recognized that primary aldosteronism may have multiple etiologies; the condition has been declared a “major public health issue” by the Endocrine Society, with recommendations for physicians to “substantially ramp up the screening of hypertensive patients.” The two major causes are a unilateral aldosterone-producing adenoma (60%) and bilateral adrenal hyperplasia or idiopathic aldosteronism (40%). Other rare causes of primary aldosteronism include unilateral primary adrenal hyperplasia, aldosterone-producing adrenal cortical carcinoma, familial aldosteronism (glucocorticoid-suppressible and idiopathic aldosteronism), and aldosterone-secreting ovarian tumors. Primary aldosteronism was historically thought to be responsible for approximately 0.5% to 2.0% of all cases of hypertension, but with the recent utilization of more extensive

and sensitive diagnostic testing, it is now estimated to be the causative factor in up to 15% of cases of hypertension. Moreover, primary aldosteronism represents 5% to 10% of surgically correctable cases of hypertension. Patients with primary aldosteronism have been shown to have cardiac, cerebrovascular, and renal dysfunction, which may be improved or reversed with appropriate treatment, thus supporting aggressive workup and treatment of patients suspected of having this disease.

Clinical Manifestations

Symptoms of primary aldosteronism are usually mild and nonspecific. The most common symptoms are headache, muscle weakness, fatigue, polydipsia, polyuria, and nocturia. Hypertension is almost always present but is often mild, with diastolic blood pressures less than 120 mm Hg in more than 70% of cases. Patients are characteristically on multiple antihypertensive medications.

Current Endocrine Society Clinical Practice Guidelines, released in May 2016, recommend biochemical evaluation for primary aldosteronism in patients with blood pressure above 150/100 mm Hg resistant to three antihypertensive medications, patients with controlled blood pressure (defined as <140/90 mm Hg) on four or more antihypertensives, and those with hypertension and one of the following: hypokalemia (spontaneous or diuretic-induced), adrenal incidentaloma, sleep apnea, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years old). In addition, it is recommended that all first-degree relatives of patients with known primary aldosteronism are recommended to be screened.

Diagnosis

Initial findings that support a diagnosis of primary aldosteronism include hypertension and spontaneous hypokalemia. However, hypokalemia has been noted to occur in less than 50% of patients with primary aldosteronism. Half of patients with an aldosterone-secreting adenoma and only 17% of patients with idiopathic aldosteronism have been shown to have a serum potassium concentration less than 3.5 mmol/L. Additional electrolyte abnormalities may include hypernatremia and a hypochloremic metabolic alkalosis. Prior to endocrine evaluation, diuretics should be

discontinued for at least 2 weeks. Plasma aldosterone/renin ration (ARR) is the initial screening test of choice, and is most accurate when performed in the morning after patients have been out of bed for at least 2 hours and have been seated for 5 to 15 minutes. A plasma aldosterone/renin ratio greater than 30 (ng/dL: ng/mL/h) along with a plasma aldosterone level greater than 20 ng/dL is sensitive and specific in the screening for, and diagnosis of, primary aldosteronism.

If aldosterone and renin determination is equivocal, confirmation of the diagnosis can be obtained using the saline suppression test or the 3-day sodium loading test; these additional diagnostic steps are unnecessary in the straightforward situation (i.e., patient with spontaneous hypokalemia, undetectable plasma renin levels, and plasma aldosterone level greater than 20 ng/dL). In the saline suppression test, 2 L of normal saline is infused intravenously over 4 hours and plasma aldosterone is measured. Confirmation of aldosteronism is obtained when the plasma aldosterone level is greater than 10 ng/dL (in the absence of primary aldosteronism, aldosterone secretion should be suppressed with saline infusion). In the 3-day sodium loading test (100 mmol NaCl per day), a 24-hour urine collection is obtained on the third day of the test to measure aldosterone, sodium, and potassium, and serum sodium and potassium are drawn simultaneously. Confirmation of aldosteronism is obtained when the urinary aldosterone is greater than 14 μg per 24 hours. In the latter test, it is important to demonstrate adequate salt loading; therefore urinary sodium should be greater than 200 mEq per 24 hours. Choice of confirmatory testing depends on patient compliance, cost, laboratory availability, and local expertise.

Imaging

Once the diagnosis of aldosteronism is established biochemically, it is critical to differentiate unilateral adrenal adenoma (60% of cases) from bilateral hyperplasia of the zona glomerulosa (idiopathic aldosteronism, 40% of cases). In patients with an aldosterone-producing adenoma, unilateral adrenalectomy corrects the hypokalemia and decreases the blood pressure in 70% of surgically treated patients. However, surgery is of little value in patients with idiopathic aldosteronism, curing hypertension in only 19% of patients. Patients with a unilateral adenoma are usually younger and have more severe hypertension, lower renin levels, higher atrial natriuretic peptide levels, higher plasma aldosterone levels, and

therefore more profound hypokalemia than patients with idiopathic aldosteronism. However, these findings alone cannot accurately differentiate patients with unilateral adenoma from those with idiopathic aldosteronism.

Endocrine Society Clinical Guidelines recommend adrenal computed tomography (CT) scan as the initial imaging modality to localize the source of aldosterone secretion. Magnetic resonance imaging (MRI) has not been shown to have an advantage over CT in determining the subtype of aldosteronism, while also being more costly and having less spatial resolution than CT. An aldosterone secreting adrenal adenoma may appear on CT as a small hypodense nodule with washout of contrast in the delayed phase at 15 minutes; however, what appears to be a microadenoma may in fact be adrenal hyperplasia or a nonfunctioning adrenal cortical nodule. Idiopathic adrenal hyperplasia (IAH) can also appear normal on CT. Rare aldosterone-producing adrenal cortical carcinomas are typically large in size (>4 cm) and have findings on imaging suspicious for malignancy. Young patients (<35 years old) with straightforward and unequivocal findings (markedly elevated aldosterone, spontaneous hypokalemia, and a unilateral lesion on CT consistent with an adenoma) can proceed straight to adrenalectomy without confirmatory testing.

In patients with no nodules, small nodules, bilateral nodules, or where the biochemical picture is not clear-cut, adrenal venous sampling (AVS) can be helpful in selecting the appropriate patients for surgical intervention and confirming the side of the functioning tumor. Adrenal venous sampling is an invasive test that requires special expertise to perform. Furthermore, difficulty in cannulating the short, right adrenal vein in particular can lead to results that are difficult or impossible to interpret. In experienced hands, complications of AVS, such as adrenal vein thrombosis, hemorrhage, adrenal infarction, and back pain, occur in approximately 2.5% of cases, and typically resolve with conservative management.

In a classic retrospective study performed at the Mayo Clinic, Young et al. selected 203 patients with primary aldosteronism and prior CT imaging for selective venous sampling. An infusion of 50 μg of cosyntropin per hour was initiated 30 minutes before catheterization of the adrenal veins by the percutaneous femoral approach. Continuous infusion of cosyntropin is utilized in order to minimize stress-induced fluctuation in aldosterone levels, maximize the gradient in cortisol between the adrenal vein and the

inferior vena cava, and maximize the secretion of aldosterone from an adenoma. Venous samples were obtained from both adrenal veins (the left-sided sample was obtained from the inferior phrenic vein near the entrance of the adrenal vein) and the inferior vena cava below the level of the renal veins. Concentrations of cortisol and aldosterone were measured in order to confirm correct catheter placement. Sampling was considered successful if the plasma level of cortisol in the adrenal vein was greater than five times that of the inferior vena cava. Aldosterone concentrations of each adrenal vein were divided by the respective cortisol concentrations to correct for an asymmetric dilutional effect between the adrenal veins. Bilateral adrenal cannulation was successful in 194 of the 203 patients. Of these 194 patients, CT correctly identified unilateral or bilateral disease in 53%. On the basis of CT findings alone, 21.7% of patients may have been incorrectly bypassed as candidates for surgery, while 24.7% may have had an unnecessary adrenalectomy. In a systematic review examining 38 studies including 950 patients, all of whom had CT or MRI in addition to AVS, CT, or MRI was inaccurate in 37.8% of patients. This study concluded that treatment decisions based on CT or MRI would have led to an inappropriate adrenalectomy in 14.6% of patients, exclusion from adrenalectomy in 19.1% of patients, and adrenalectomy on the incorrect side in 3.9% of patients. In light of these results and others, AVS can contribute to treatment decisions in as many as 50% of patients. A cortisol-corrected aldosterone ratio from “high-side” to “low-side” of greater than 4:1 indicates unilateral aldosterone secretion, while a ratio of less than 3:1 (or elevated ratios on both sides and a similar response to ACTH stimulation) suggests bilateral aldosterone hypersecretion. Factors that have been shown to be associated with successful lateralization by AVS include a low plasma renin level, high plasma aldosterone: renin ratio, and a lesion on CT of at least 3 cm in size. The use of ACTH stimulation and confirmation of catheter positioning by an adrenal: peripheral cortisol level of >5 are associated with the highest rates of lateralization. Using these criteria, a sensitivity of 95% and a specificity of 100% has been reported.

AVS is technically unsuccessful in approximately 20% of cases, although this number improves with increasing radiologist experience. In particular, this is due to difficulty in cannulating the right adrenal vein, the rate of which can be as low as 30% in low-volume centers. Despite this, Pasternak et al. demonstrated that cannulation of the left adrenal vein only can still often predict laterality; patients with a left adrenal vein to inferior

vena cava (LAV/IVC) aldosterone ratio of greater than 5.5 are likely to have left-sided hypersecretion, while those with a ratio less than 0.5 are likely to have right-sided hypersecretion (due to suppression of the contralateral gland).

Our current approach to the evaluation of patients suspected of having primary aldosteronism is shown in Figure 16.2.

Treatment

The treatment of primary aldosteronism depends on the etiology. Bilateral adrenal hyperplasia is usually best managed medically using the aldosterone antagonist spironolactone. Side effects of spironolactone, including gynecomastia, erectile dysfunction, menstrual disturbances, and muscle cramps can limit patient compliance. Most patients can achieve adequate control of their blood pressure with this medication alone or in conjunction with other antihypertensives.

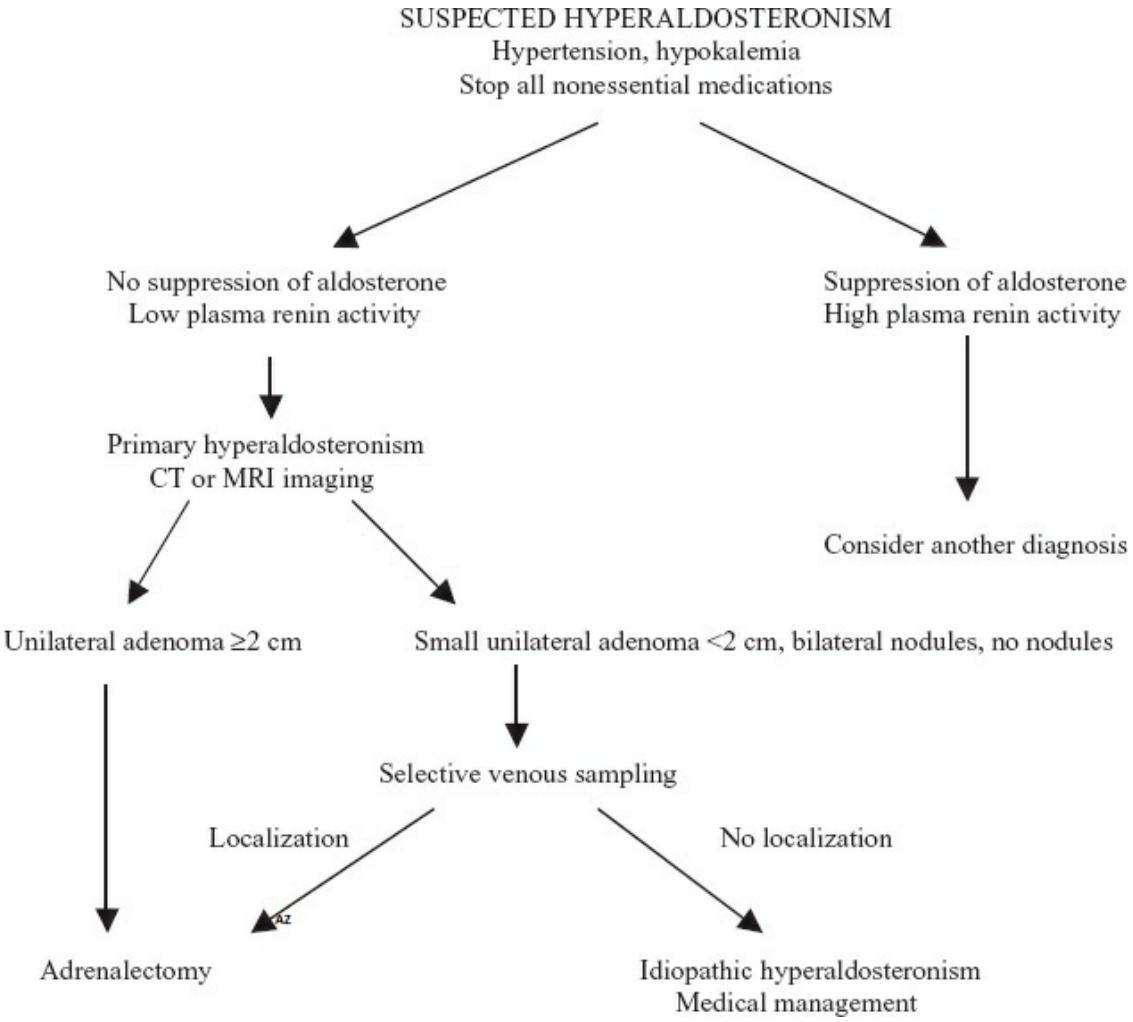

Figure 16.2 An algorithm for the evaluation of the patient with suspected primary aldosteronism.

When an aldosterone-producing adenoma or unilateral adrenal hyperplasia is diagnosed, the appropriate treatment remains surgical resection. Unilateral adrenal hyperplasia cannot be differentiated from an adenoma preoperatively; nevertheless, the treatment is the same. Preoperatively, patients should be placed on spironolactone and given potassium supplementation to help normalize fluid and electrolyte balance over a 3- to 4-week period.

Normalization of hypokalemia, aldosterone levels, and plasma aldosterone: renin ratio occurs in nearly 100% of patients with a unilateral aldosteronoma postoperatively. Up to 70% of patients will have resolution of hypertension after adrenalectomy, while 30% will require continued management with antihypertensive medications. Even those who require continued antihypertensive therapy will usually require fewer medications for adequate blood pressure control compared to preoperatively. Factors predictive of improvement or cure of hypertension after adrenalectomy include female gender, younger age, lower preoperative renin levels, shorter duration of hypertension (indicating that long-standing cardiovascular effects occur independent of aldosterone levels), and fewer antihypertensive medications preoperatively. Patients with primary aldosteronism have been shown to be at increased risk of cardiovascular and renal complications, including arrhythmias, myocardial infarction, stroke, chronic kidney disease, and death. Adrenalectomy decreases left ventricular diameter, volume, and workload, improves carotid artery stiffness, and reverses albuminuria. Adrenalectomy has also been shown to be more cost-effective than lifelong medical therapy in patients with primary aldosteronism amenable to surgical resection.

Since nearly all patients with aldosteronomas have relatively small tumors which are universally benign, they are usually excellent candidates for a minimally invasive approach. Surgical resection can be performed either through a transabdominal laparoscopic or a retroperitoneoscopic approach. While the standard surgical approach for patients with an aldosteronoma is unilateral adrenalectomy, adrenal-sparing surgery (partial adrenalectomy) has been applied in selected patients with good results. Approximately 2% or less of adrenal cortical carcinomas cause isolated aldosteronism. In the very rare situation of a patient presenting with aldosteronism and a large adrenal mass, an open anterior approach should

be used to facilitate complete resection (see the section on adrenal cortical carcinoma).

CORTISOL-PRODUCING ADRENAL ADENOMA

Introduction

Cushing syndrome was first described by Harvey W. Cushing in 1932, and refers to a state of hypercortisolism that can result from a number of different pathologic processes (Table 16.1). Cortisol regulation involves feedback loops through the pituitary gland and hypothalamus. The most common cause of Cushing syndrome is exogenous steroid administration. After exclusion of patients taking exogenous steroids, approximately 70% of the remaining cases of hypercortisolism are secondary to hypersecretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, a condition known as Cushing disease. Cushing disease is usually caused by a small pituitary adenoma (<1 cm). Ectopic secretion of ACTH, referred to as ectopic ACTH syndrome, is the cause of approximately 15% of cases of Cushing syndrome. Ectopic ACTH syndrome is caused by malignant tumors in 80% of cases. Carcinoma of the lung accounts for nearly three-quarters of cases, with the remaining cases being caused by carcinoma of the pancreas, carcinoid tumors, medullary thyroid cancer, pheochromocytoma, and other neuroendocrine tumors. Ectopic secretion of corticotropin-releasing factor is exceedingly rare but has been reported in a few cases.

TABLE 16.1 Common Causes of Cushing Syndrome

Exogenous steroids
Cushing disease (due to pituitary adenoma)
Adrenal tumors
Adrenal cortical adenoma
Adrenal cortical carcinoma
Primary adrenal cortical hyperplasia
Ectopic adrenocorticotropin syndrome
Ectopic corticotropin-releasing factor syndrome

Hypersecretion of cortisol from the adrenal glands (ACTH-independent)

accounts for approximately 10% to 20% of cases of Cushing syndrome. The underlying cause is an adrenal adenoma 50% to 60% of the time and adrenal cortical carcinoma 20% to 25% of the time. Bilateral adrenal hyperplasia accounts for the remaining 20% to 30% of cases.

Clinical Manifestations

Weight gain is the most common feature of hypercortisolism and occurs predominantly in the truncal area. This centripetal obesity, combined with muscle wasting in the extremities, fat deposition in the head and neck region (“moon facies”), and dorsal kyphosis (“buffalo hump”) gives the patient a characteristic body habitus. Abdominal striae, hypertension, hyperglycemia, depression, bruising, osteoporosis and menstrual irregularities can also occur. Children with Cushing syndrome have weight gain in association with decreased linear growth. Several studies have demonstrated that 2% to 3% of patients with poorly controlled diabetes mellitus have confirmed Cushing syndrome, while 5.8% of patients seen in endocrinology clinics for diabetes, hypertension, or polycystic ovarian syndrome are eventually shown to have Cushing syndrome. Similarly, approximately 10% of patients with osteoporosis and a vertebral fracture were found to have Cushing syndrome. In some patients with Cushing syndrome due to an adrenal cortical tumor, these signs may be subtle or even absent altogether (“Subclinical Cushing Syndrome,” discussed later in this section). Adrenal cortical carcinomas can produce cortisol but often also produce androgens, resulting in virilization and hirsutism.

Diagnosis

Patients with Cushing syndrome have been shown to have an increased risk of cardiovascular and infectious complications, thus stressing the importance of early diagnosis and treatment.

The evaluation for Cushing syndrome should be aimed at establishing the diagnosis first and then determining the etiology. To establish the diagnosis, a state of hypercortisolism must be documented. Endocrine Society Clinical Practice Guidelines currently recommend first taking a thorough medication history, followed by testing of any patient with unusual features for age or multiple and progressive features (described above), in children with decreasing height and increasing weight, and in patients with an incidentally discovered adrenal mass.

The adult adrenal glands secrete on average 10 to 30 mg of cortisol each day. The secretion follows a diurnal variation: cortisol levels tend to be high early in the morning and low in the evening. The most sensitive initial screening test for hypercortisolism in patients with an adrenal mass is an overnight 1-mg dexamethasone suppression test (described below). Documentation of lack of cortisol suppression following 1 mg of dexamethasone should be followed by measurement of 24-hour urinary-free (un-metabolized) cortisol; the normal level is generally below 80 μg/day. In addition, to determine the etiology of an elevated cortisol level, plasma ACTH levels should be checked. Secretion of ACTH also follows a diurnal variation, preceding that of cortisol by 1 to 2 hours. Suppressed levels of ACTH are seen in patients with functional adrenal adenomas, adrenal cortical carcinomas, or autonomously functioning adrenal hyperplasia. In such cases, autonomous secretion of cortisol by the pathologic process within the adrenal gland inhibits pituitary ACTH release ("ACTH-independent Cushing syndrome"). Patients with Cushing disease (i.e., a pituitary adenoma-secreting ACTH) usually have plasma ACTH levels that are elevated or within the upper limits of normal ("ACTH-dependent Cushing syndrome"). When there is an ectopic source of ACTH secretion, for example, with a metastatic tumor process, the plasma ACTH level is usually markedly increased.

The most sensitive standard method for detecting hypercortisolism is the overnight one milligram dexamethasone suppression test. One milligram of dexamethasone is taken orally at 10:00 or 11:00 PM. The vast majority of normal individuals will suppress their cortisol level to <5 μg/dL at 8:00 AM the following morning. Failure to suppress the 8:00 AM cortisol level to less <5 μg/dL is consistent with hypercortisolism. This test has a false-negative rate of only 3% but unfortunately a false-positive rate of up to 30%. While a normal overnight dexamethasone suppression test excludes clinically significant hypercortisolism, an abnormal test result does not necessarily establish the presence of hypercortisolism but does require further investigation. Many experts currently propose further testing even in patients with serum cortisol values between 1.8 and 5 μg/dL to increase the detection of subclinical hypercortisolism (see below). Naturally, when lower cutoffs are used, specificity decreases, yielding more false positives. Since false-positive results are common, patients with elevated cortisol levels following overnight testing should undergo further evaluation by obtaining 8 AM cortisol and ACTH levels along with 24-hour urine

collection for urinary-free cortisol. The 24-hour urinary-free cortisol is somewhat less sensitive than overnight dexamethasone suppression but more specific. In patients who have obvious signs or symptoms of hypercortisolism, a timed urinary collection should be obtained for cortisol determination. It is recommended that patients submit at least two urine collections and the first morning void should be discarded. Again, the normal level of urinary-free cortisol is <80 μg/day. This test is not as accurate in patients with renal failure and those in the second and third trimesters of pregnancy. Importantly, dehydroepiandrosterone sulfate levels will typically be low in patients with ACTH suppression from autonomous cortisol secretion by an adrenal mass.

In equivocal cases, a formal 2-day low-dose dexamethasone test may be performed to detect the presence of cortisol overproduction by an adrenal tumor. A dose of 0.5 mg of dexamethasone is administered every 6 hours for 2 days with pre- and postdexamethasone 24-hour urinary-free cortisol levels. Alternatively, individuals with failure of suppression after the 1-mg overnight dexamethasone test may be subjected to a higher dose (3 or 8 mg overnight suppression). Patients with true autonomous secretion of cortisol should continue to exhibit nonsuppression with these higher doses of dexamethasone.

In patients who are found to have ACTH-independent Cushing syndrome, CT or MRI of the adrenal gland should be performed to localize the source of hypercortisolism. In patients with ACTH-dependent Cushing syndrome (ACTH levels not suppressed with dexamethasone), chest CT and MRI can be performed, followed by bilateral petrosal sinus sampling. CT or MRI of the sella turcica can also be used prior to surgical resection of a pituitary tumor.

Treatment

The appropriate management of Cushing syndrome depends on the underlying etiology. Patients with Cushing disease should undergo transsphenoidal hypophysectomy of the pituitary adenoma when it is believed to be resectable. Pituitary irradiation may also be used when resection is not curative, or otherwise judged not to be indicated. Patients with ectopic ACTH syndrome should have the underlying malignant condition identified and treated. Bilateral adrenalectomy is only occasionally indicated for patients with Cushing syndrome and should be reserved for those who fail to respond to standard management, including

medical therapy and transsphenoidal hypophysectomy, in those with an unresectable primary or metastatic cancer causing ectopic ACTH production, and in those who experience end-organ injury from the consequences of overt hypercortisolism. Recent data from our institution demonstrate that in patients with ACTH-dependent hypercortisolism (either from a pituitary lesion or ectopic secretion) resistant to other treatment options, bilateral adrenalectomy can improve metabolic disturbances and minimize adverse effects related to medical therapies. However, careful patient selection is essential, as these patients typically have poor performance status prior to surgery and limited overall survival. Patients with autonomously functioning bilateral adrenal hyperplasia usually require bilateral total adrenalectomy. If bilateral adrenalectomy is performed, patients require not only perioperative steroid coverage (Tables 16.2 and 16.3) but also lifelong replacement of both glucocorticoids and mineralocorticoids. Bilateral adrenalectomy can be performed laparoscopically, retroperitoneoscopically, via an open posterior retroperitoneal approach, or via open laparotomy. Our current preferred approach for the majority of these patients is via a minimally invasive retroperitoneoscopic approach when body habitus and adrenal size will permit.

TABLE 16.2 Recommendations for Perioperative Glucocorticoid Coverage

Surgical Stress	Examples	Hydrocortisone Equivalent (mg)	Duration (days)
Minor	Inguinal herniorrhaphy	25	1
Moderate	Open cholecystectomy	50–75	1–2
	Lower-extremity revascularization		
	Segmental colon resection		
	Total joint replacement		
	Abdominal hysterectomy		
Major	Pancreaticoduodenectomy	100–150	2–3
	Esophagogastrectomy		
	Total proctocolectomy		
	Cardiac surgery with cardiopulmonary bypass		

TABLE 16.3 Comparison of Common Steroid Preparations

Steroid	Half-Life (hours)	Glucocorticoid Activity (Relative to Cortisol)	Mineralocorticoid Activity (Relative to Cortisol)
Cortisol	8–12	1	1
Cortisone	8–12	0.8	0.8
Prednisone	12–36	4	0.25
Prednisolone	12–36	4	0.25
Methylprednisolone	12–36	5	0
Triamcinolone	12–36	5	0
Betamethasone	36–72	25	0
Dexamethasone	36–72	30–40	0

Patients with a cortisol-producing neoplasm of the adrenal gland, whether the tumor represents an adenoma or a carcinoma, should undergo resection of the involved adrenal gland. Although almost all adenomas can be resected, adrenal cortical carcinomas that secrete cortisol are resectable in only 25% to 35% of patients. Combination chemotherapy, as well as adrenolytic treatment with mitotane, has demonstrated activity in patients with unresectable or metastatic adrenal cortical carcinoma, but neither treatment is considered curative. Symptoms related to hypercortisolism in patients with metastatic or unresectable functioning tumors can sometimes be minimized with a variety of agents that are toxic to adrenal tissue or interfere with steroid hormone synthesis, including mitotane as well as aminoglutethimide, metyrapone, or ketoconazole.

Subclinical Cushing Syndrome

Subclinical Cushing syndrome, also called “subclinical autonomous glucocorticoid hypersecretion,” is a state of hypercortisolism without the associated overt clinical findings or phenotype of Cushing syndrome. Subclinical Cushing syndrome may occur in up to 20% of patients with apparently incidental adrenal tumors. Although these patients by definition do not have overt signs and symptoms of Cushing syndrome, further questioning often elucidates a history of hypertension, weight gain, and hyperlipidemia. There are currently no “gold standard” criteria to diagnose subclinical Cushing syndrome, but the best screening test to identify the

possible presence of the condition remains an overnight 1-mg dexamethasone suppression test. A morning serum cortisol level of <1.8 µg/dL indicates appropriate suppression and excludes hypercortisolism, while a level above that indicates the possible presence of subclinical Cushing syndrome in patients without typical signs and symptoms. Late-night salivary cortisol testing is an alternative for patients suspected of having clinical (classic) or subclinical Cushing syndrome, and as a confirmatory test is currently more popular than the 48-hour dexamethasone test. Changes in serum cortisol are mirrored in salivary cortisol levels within minutes. This test is easy to perform, noninvasive, and has been shown to be particularly useful in children with suspected Cushing syndrome. In this test, patients are asked to give a saliva sample on two separate evenings between 11:00 PM and midnight. Saliva is collected via either passive drooling into a tube or having the patient chew on a cotton pledget for 1 to 2 minutes. Patients without classic or subclinical Cushing syndrome should exhibit a normal circadian variation in cortisol secretion, with a salivary cortisol level of less than 145 ng/dL at midnight, while patients with autonomous, abnormal cortisol secretion should have higher salivary levels.

General recommendations are for adrenalectomy in young patients with a unilateral adrenal nodule with imaging characteristics consistent with an adrenal adenoma and documented or suspected subclinical Cushing syndrome, particularly in the presence of suggestive metabolic disturbances (hypertension, hyperlipidemia, obesity, diabetes, osteoporosis). Several studies have demonstrated trends toward improvement and/or resolution of these comorbidities after surgical resection, in addition to an improvement in reported quality of life. Importantly, patients with subclinical Cushing syndrome may require peri- and postoperative glucocorticoid replacement (Tables 16.2 and 16.3), as the ACTH suppression secondary to the hypercortisolism can result in atrophy of the contralateral adrenal gland, often resulting in symptoms of adrenal insufficiency upon removal of the affected gland. Steroids, if required postoperatively, can typically be tapered within 6 to 12 months postoperatively.

PHEOCHROMOCYTOMA

Introduction

Pheochromocytomas represent a potentially curable form of endocrine hypertension that, if untreated, places patients at high risk for morbidity and mortality, particularly during surgery and pregnancy. Pheochromocytomas are neuroectodermal tumors that arise from the chromaffin cells of the adrenal medulla. Ten percent of neuroectodermal chromaffin-cell tumors are located in an extra-adrenal site (carotid bulb, mediastinum, abdomen, pelvis, urinary bladder, renal hilum, and organ of Zuckerkandl [located between the inferior mesenteric artery and aortic bifurcation]), and are called paragangliomas. The estimated incidence of pheochromocytoma and paraganglioma is between 0.005% and 0.1% of the general population and between 0.1% and 0.3% of the adult hypertensive population. Approximately 10% of adrenal pheochromocytomas are bilateral, with some patients presenting with multiple tumors. Pheochromocytomas represent 5% of incidentally discovered adrenal masses.

Histologic evidence of malignancy can be demonstrated in 5% to 10% of pheochromocytomas and 15% to 35% of paragangliomas. Invasion of adjacent organs and/or the presence of metastatic disease are the defining features of malignancy, which can be difficult or impossible to distinguish histologically. Metastatic disease most commonly occurs in the bones, liver, lungs, kidneys, and lymph nodes. Local recurrence after surgical resection occurs in 6.5% to 16.5% of patients. Metastatic disease, if it occurs, is most commonly present at diagnosis, but has been documented to occur as late as 40 years after the original diagnosis.

Genetics

Historically, familial pheochromocytomas have been estimated to account for approximately 10% of cases (“the 10% rule”); however, recent data suggest that 40% or more of unselected cases of apparently sporadic pheochromocytomas are in fact hereditary. Genetic alterations associated with pheochromocytoma are listed in Table 16.4.

Multiple endocrine neoplasia (MEN) type IIA and IIB are associated with pheochromocytomas. MEN IIA is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism, although only one-third of patients with MEN IIA develop a clinically significant pheochromocytoma. However, it is recognized that patients with MEN IIA can develop small, subclinical pheochromocytomas or bilateral adrenal medullary hyperplasia. Mutations in codon 634 (C634) of

exon 11 of the RET proto-oncogene are particularly associated with this feature. The penetrance of pheochromocytoma (either unilateral or bilateral) in patients with C634 mutations in MEN IIA is nearly 100%, indicating that MEN IIA patients with an RET C634 mutation should be screened for pheochromocytoma early and often. Fortunately, the risk of malignant pheochromocytoma in these patients is very low; no more than 5%. The risk for inherited pheochromocytoma in patients with MEN I is very low, but has been observed in these patients, albeit extremely rarely (<1% of patients with MEN I).

Neuroectodermal dysplasias consisting of neurofibromatosis, tuberous sclerosis, Sturge–Weber syndrome, and von Hippel–Lindau disease are also associated with pheochromocytomas. The risk for inherited pheochromocytomas is very low in neurofibromatosis type 1 (<1%). Pheochromocytoma can also occur in hereditary paraganglioma syndromes (mutations in succinate dehydrogenase *SDHD, SDHB, SDHC*, and *SDH5* genes), with those tumors with mutations in subunit B (SDHB) having a particularly high risk of malignancy (34% to 83%). Hereditary paraganglioma syndromes predispose to both extra-adrenal and adrenal paragangliomas. Patients with familial pheochromocytoma syndromes require follow-up and periodic screening for pheochromocytoma, especially before any planned surgical procedure.

The tumor suppressor genes nm23-H1, TIMP-4, BRMS-1, TXNIP, CRSP-3, and E-Cad, have been demonstrated to be down-regulated in malignant pheochromocytomas. Ki-67, a nuclear antigen used as a marker of proliferation in a variety of tumors, has been examined in pheochromocytoma. A Ki-67 index of greater than 3% can help distinguish between benign and malignant pheochromocytomas and may predict malignant potential.

TABLE **16.4** Major Genetic Alterations Associated with Pheochromocytoma/Paraganglioma

Syndrome	Gene	Features	Frequency	Malignant Potential
NF1	*NF1*	Von Recklinghausen disease: peripheral nervous system tumors, gastrointestinal stromal tumors, malignant gliomas, breast cancer, leukemia	1% of all pheo/PGL patients 1–14% of patients with NF1 develop pheo/PGL	7–11%
VHL	*VHL*	Von Hippel–Lindau disease: retinal and cerebellar hemangioblastoma, renal cell carcinoma, pheo/PGL (multiple, bilateral), pancreatic neuroendocrine tumors	5–10% of all pheo/PGL patients 20% of patients with VHL develop pheo/PGL	<10%
MENIIA/B	*RET*	MENIIA: medullary thyroid carcinoma, pheochromocytoma (bilateral), hyperparathyroidism MENIIB: medullary thyroid carcinoma, pheochromocytoma (bilateral), mucosal neuromas	5% of all pheo/PGL patients 50% of MEN2A patients develop pheo/PGL	3–5%
PGL1	*SDHD*	Multiple pheo and PGL (particularly head and neck), nonmedullary thyroid carcinoma, gastrointestinal stromal tumors	5–10% of all pheo/PGL patients	Rare
PGL2	*SDH5*	Pheo and PGL	Unknown	Benign
PGL3	*SDHC*	Pheo and PGL (particularly head and neck), nonmedullary thyroid carcinoma, gastrointestinal stromal tumors	Rare	Rare
PGL4	*SDHB*	Solitary pheo and PGL, renal cell carcinoma, nonmedullary thyroid carcinoma, gastrointestinal stromal tumors	10–15% of all patients with pheo/PGL	30–70% malignant

Pheo, pheochromocytoma; PGL, paraganglioma.

As mentioned above, recent and evolving data suggest that up to 40% or more of cases of pheochromocytomas or paragangliomas are hereditary. A

hereditary syndrome should be suspected when patients are found to have a pheochromocytoma at a young age, bilateral or recurrent disease, or extra-adrenal disease. Several authors recommend genetic screening, or at least referral to a trained genetic counselor, for all patients with pheochromocytoma. Patients who have a family history of pheochromocytoma or paraganglioma or an associated clinical syndrome based on evaluation by a genetic counselor are found to have a mutation in 90% of cases. Due to the cost of extensive genetic testing, a targeted and systematic approach to genetic testing has been proposed. First, genetic testing should be based on any familial or syndromic features, particularly RET, VHL, NF-1, and SDH genes. In the case of malignant disease, SDHB testing should follow. For bilateral tumors, VHL and RET genes should be tested first, and in patients with extra-adrenal disease, testing for SDHD and SDHB genes should be performed. Once a mutation is found, no further testing is recommended, as the chance of two genetic mutations occurring is uncommon. Once a mutation is identified, family members should be tested. High-risk patients in whom a genetic mutation is suspected but not identified should still be followed regularly with annual physical examination, biochemical testing, and imaging; repeat genetic testing can be considered as technologies improve and new mutations are identified.

Clinical Manifestations

Hypertension, sustained or paroxysmal, is the most common clinical presentation of pheochromocytoma. Paroxysmal elevations in blood pressure can vary markedly in frequency and duration and can be initiated by a variety of events, including heavy physical exertion and eating foods high in tyramine (e.g., chocolate, cheese, red wine). Other common symptoms include excessive sweating, palpitations, arrhythmias, tremulousness, anxiety, headache, chest pain, nausea, and vomiting. More than half of patients with pheochromocytomas have impaired glucose tolerance and may have symptoms of diabetes mellitus, including polydipsia or polyuria. These signs and symptoms are secondary to the excess catecholamine secretion by the tumors and resolve with tumor resection. Patients with functioning tumors are rarely asymptomatic (<10% of patients); an exception is patients with hereditary pheochromocytomas. Nonfunctioning adrenal pheochromocytomas are rare; extra-adrenal paragangliomas, however, may be nonfunctioning. Patients with

incidentally discovered pheochromocytoma tend to have higher rates of nonspecific symptoms (abdominal and back pain), lower rates of “classic” pheochromocytoma symptoms, are older than symptomatic patients, and are less likely to have an associated genetic syndrome.

Diagnosis

The diagnosis of pheochromocytoma is made by documenting excess secretion of catecholamines. Increased levels of catecholamines or their metabolites are seen in more than 90% of patients with pheochromocytoma. The adrenal glands and the organ of Zuckerkandl produce the enzyme phenylethanolamine-*N*-methyl-transferase, which converts norepinephrine to epinephrine. Pheochromocytomas that arise elsewhere do not contain this enzyme and thus do not produce much, if any, epinephrine. As a result, extra-adrenal pheochromocytomas (paragangliomas) secrete predominantly dopamine and norepinephrine.

Plasma-free metanephrine determination is a very sensitive screen for the presence of catecholamine elevation and is more convenient than timed urine collection. Plasma normetanephrines have also been shown to correlate with a diagnosis of pheochromocytoma. Twenty-four-hour urine collection for free catecholamine levels (dopamine, epinephrine, and norepinephrine) and their metabolites (normetanephrine, metanephrine, vanillylmandelic acid) was the original test of choice; it can still be useful in confirming suspected catecholamine elevation identified by plasma screen. A scoring system has been proposed by Carr et al., which includes elevated levels of normetanephrine (>1.7 times greater than normal) and metanephrine (>1.34 times greater than normal), age less than 50, and tumor size larger than 3.3 cm on imaging; a score of 4 or higher has a specificity and positive predictive value of 100% in diagnosing pheochromocytoma. Patients with incidentally discovered pheochromocytoma have lower values in all markers, both plasma and urine. Patients with malignant pheochromocytoma tend to have significantly increased levels of dopamine in their 24-hour urine collection. Clinicians should be aware of common agents and medications that can cause false-positive results, including caffeine, nicotine, tricyclic antidepressants, monoamine oxidase inhibitors, phenoxybenzamine, calcium channel blockers, levodopa, alpha-methyldopa, ephedrine, and acetaminophen.

Once the diagnosis of pheochromocytoma is made, localization studies

can be carried out. A review of preoperative imaging in a large series of histologically confirmed pheochromocytomas found that MRI was the most sensitive modality (98%), followed by CT imaging (89%) and ^{131}I-metaiodobenzylguanidine (MIBG) scanning (81%). High-quality CT can detect up to 95% of adrenal masses larger than 6 to 8 mm and is usually the initial imaging study of choice; it is rare for a clinically significant primary pheochromocytoma to not be imaged by CT. On CT, a pheochromocytoma will typically be distinguished from a cortical adenoma in part by having a greater overall tissue density (precontrast Hounsfield units of >10). MRI may be useful in selected cases because the T2-weighted images can identify chromaffin tissue; the T2-weighted adrenal mass-to-liver ratio of pheochromocytomas or paragangliomas is usually more than 3. In contrast, MRI findings consistent with an adrenal adenoma are a high T1 and low T2 signals relative to the liver and spleen. This ratio is also higher than that typical of adrenal cortical carcinomas and metastases to the adrenal gland.

MIBG scan is another imaging modality that can be helpful in localizing extra-adrenal, metastatic, or bilateral pheochromocytomas. This radiolabeled amine is selectively picked up by chromaffin tissue and can identify the majority of pheochromocytomas, regardless of their location. Therefore, MIBG scanning is useful in patients with biochemical evidence of pheochromocytoma whose tumors cannot be localized by CT or MRI and in the follow-up evaluation of patients with suspected or documented recurrent or metastatic disease.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (FDG PET) has recently been examined as an alternative to MIBG, CT, or MRI. Timmers et al. found that FDG PET was equally effective in detecting nonmetastatic pheochromocytomas and paragangliomas when compared to MIBG, but was more sensitive in detecting metastatic disease. The authors also found that FDG PET was superior in localizing bone metastases when compared to both CT and MRI. Tumors with SDHB mutations, which are particularly prone to malignancy and metastases, are frequently identified on FDG PET. Due to its ubiquity and high sensitivity, FDG PET has become the imaging procedure of choice for staging of patients with recurrent or metastatic pheochromocytoma or paraganglioma.

The histopathology-defined Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) has been proposed to separate benign and malignant tumors. PASS includes 12 histopathologic characteristics, including large

nests of diffuse growth, necrosis, cellularity, spindling, mitotic figures, vascular and capsular invasion, and nuclear pleomorphism and hyperchromasia. Components of the PASS were more common in larger tumors and patients with higher levels of metanephrines and normetanephrines. A PASS greater than 4, and in particular greater than 6, has been associated with malignancy and suggests a patient should be followed closely for recurrence.

Treatment

After diagnosis and localization of the pheochromocytoma, careful preoperative preparation is required to prevent a cardiovascular crisis during surgery caused by excess catecholamine secretion. The main focus of preoperative preparation is adequate alpha-adrenergic blockade and restoration of fluid and electrolyte balance. The practice of alpha blockade originated in 1956, when Priestly and colleagues resected 51 pheochromocytomas using intraoperative alpha blockade without mortality. Phenoxybenzamine remains the most commonly used alpha-adrenergic blocking agent and is usually begun at a dose of 10 mg twice a day. The dosage is gradually increased over a 2- to 3-week period until adequate blockade is reached to the point of postural hypotension. The total dose used should not exceed 1 to 2 mg per kg per day. Calcium channel blockade may be added in cases of resistant hypertension. Beta blockade following alpha blockade may help prevent tachycardia and other arrhythmias. Beta blockade should not be instituted unless alpha blockade has been established; otherwise, the beta blocker will inhibit epinephrine-induced vasodilation, leading to more significant hypertension and left heart strain. In addition to requiring pharmacologic preparation, patients with pheochromocytoma require correction of volume depletion as well as any concurrent electrolyte imbalances. We encourage patients to salt-load the week prior to operation.

The perioperative management of patients with pheochromocytoma can be challenging, but is generally safely accomplished in experienced centers. Rarely is alpha-adrenergic blockade complete prior to surgical resection. The anesthesiologist should be prepared to treat a hypertensive crisis with sodium nitroprusside, nitroglycerine, or nicardipine, while tachyarrhythmias should be treated with either a beta-blocker or antiarrhythmics. Hypotension should first be treated with volume expansion, followed by vasopressor agents such as norepinephrine,

phenylephrine, and vasopressin. Magnesium results in vasodilatation and inhibits catecholamine release from the adrenal medulla while blocking catecholamine receptors. Lower preoperative dose of phenoxybenzamine or preoperative use of selective alpha blockade, larger tumors, open procedures, and intraoperative use of vasopressin are associated with increased intraoperative hemodynamic instability. Commonly used preoperative and perioperative medications are listed in Table 16.5.

If preoperative imaging suggests a modestly sized, benign-appearing unilateral pheochromocytoma with a radiographically normal contralateral gland, we currently prefer a unilateral laparoscopic or posterior retroperitoneoscopic approach. A minimally invasive approach is also appropriate for patients with MEN II or von Hippel–Lindau disease with a small, unilateral pheochromocytoma less than approximately 6 cm in size. For patients with MEN II or von Hippel–Lindau disease with bilateral disease, a bilateral minimally invasive approach may also be appropriate. Cortical-sparing adrenalectomy, either open or laparoscopic, has been performed successfully in patients with MEN II or von Hippel–Lindau disease with bilateral pheochromocytomas, avoiding chronic steroid hormone replacement and the risk of addisonian crisis in most patients. In general, at least one-third of one adrenal gland must be preserved with its blood supply in order to reliably prevent adrenal insufficiency. For tumors greater than 6 cm in size open adrenalectomy is generally preferred, although experienced surgeons may apply an individualized approach. Obesity and concern for malignancy based on imaging are relative contraindications to a minimally invasive procedure. Paragangliomas may also be approached in a minimally invasive fashion from either a retroperitoneoscopic approach or an anterior approach, depending on the details of the tumor and patient anatomy and surgeon experience and preference. Whatever the approach, the surgeon should manipulate the tumor as little as possible and ligate the tumor’s venous outflow via the adrenal vein as early in the procedure as practical (while recognizing that early division of the vein without concomitant division of arterial inflow may increase venous congestion of the tumor and back-bleeding).

Postoperatively, patients should be monitored carefully for 24 to 48 hours so that they can be observed for arrhythmias, as well as hypotension secondary to compensatory vasodilation. Hypoglycemia may result from decreased glucose production from a drop in circulating catecholamines. Hypertension may persist postoperatively in 25% of patients, especially in

those with sustained hypertension preoperatively.

While follow-up after resection of pheochromocytoma or paraganglioma has not been completely standardized, Press et al. recommend measurement of plasma-free metanephrines at 1, 6, and 12 months postoperatively, then annually thereafter, in addition to yearly cross-sectional imaging. Biochemical testing should include a plasma-free metanephrine level or timed urine collection for catecholamine determination to exclude recurrence. If recurrence is suspected based on biochemical evaluation, localizing studies should be performed as discussed above, and resection of recurrent tumor is indicated when feasible.

TABLE 16.5 Common Medications Used in the Management of Pheochromocytoma

Medication	Standard Dosage	Contraindication	Main Drug Interaction	Main Side Effects	Comments
Phenoxybenzamine (nonselective α-blocker)	10 mg BID-TID	Conditions compromised by hypotension	Reports of hypertensive episodes when used in combinations with β-blockers	Orthostatic hypotension, nasal stuffiness, tachycardia, hypoglycemia, miosis, sexual dysfunction, somnolence	May be increased to 20–40 mg/day to total dose of 1–2 mg/kg/day BID-TID; start 10–14 days before surgery
Doxazocin (selective α1-blocker)	5 mg daily	Hypersensitivity to product or quinazolines	β-blockers, verapamil	Hypotension, tachycardia, dizziness	Less expensive, more readily available than phenoxybenazmine
Metyrosine (tyrosine hydroxylase inhibitor)	250 mg TID-QID, with doses titrated by 250–500 mg to maximum of 1.5–4 g/d	Hypersensitivity to metyrosine products	Minimal	Crystalluria, extrapyramidal effects, diarrhea, anxiety, drowsiness, sedation, depression, nightmares. Long-term use can result in heart failure.	Best used for epinephrine-only secreting tumors, or in patients with contraindications to β-blockade. Best to limit use to the perioperative period due to cardiac toxicity. Given as a half dose the morning of surgery.
Propranolol (nonselective β-blocker)	10–40 mg BID-TID	Lack of α-blockade, second- or third-degree atrioventricular block, congestive heart failure, myocarditis, hypersensitivity, asthma	Can interact with other cardiac medications, antidiabetic medications, cimetidine, fentanyl, rifampin, theophylline	Bradycardia, bronchospasm, depression, diarrhea	Should only be used to treat tachyarrhythmias once α-blockade complete

Nicardipine (calcium channel blocker)	20 mg TID or 30 mg BID	Aortic stenosis, angina, congestive heart failure	β-blockers	Heart block/bradycardia, hypotension, dizziness, edema, drowsiness	Used in patients with inadequate blood pressure control with α-blockade or in those who cannot tolerate α-blockade, also decreases coronary vasospasm
Nitroprusside (direct vasodilator)	2–4 μg/kg/min	Hypersensitivity, anemia, optic atrophy, head trauma, tobacco amblyopia	Sildenafil (a phosphodiesterase inhibitor, which potentiates hypotensive effects)	Hypotension, headache, methemoglobinemia, cyanide toxicity	Dilute in D5W only. With prolonged infusion (>24 hours), patients can develop cyanide toxicity. Dose reduced in patients with liver or renal impairment
Esmolol (β-blocker)	Titrate to effect (12–200 μg/kg/min)	Hypersensitivity, bradycardia, atrioventricular block, and cardiogenic shock	Fentanyl, cardiac medications	Hypotension, bradycardia	Short duration of action (half-life 10 minutes)
Norepinephrine (α-agonist)	4–16 μg/min as an infusion	Hypovolemia	Tricyclic antidepressants, cardiac medications	Hypertension, decreased visceral perfusion, anxiety, nausea, vomiting, urinary retention, cardiac arrhythmias	Avoid subcutaneous extravasation
Epinephrine (β-agonist)	0.1–0.2 mg/kg	Hypersensitivity, dilated cardiomyopathy, coronary artery disease, narrow-angle glaucoma, hypovolemic shock, intra-arterial injection, labor	Cardiac medications, halothane, tricyclic antidepressants	Hypertension, nausea, vomiting, headache, cardiac arrhythmias, tachycardia	Limited utility

The most common sites of metastases from malignant pheochromocytoma are bone, liver, and lungs, and less commonly, regional lymph nodes. Patients with known or suspected malignant pheochromocytoma should be staged with standard imaging studies as well as MIBG scanning. Therapy should be individualized based upon the extent of disease. Resection of malignant pheochromocytoma, including resection of metastases, may be considered in good-risk individuals if the metastases are limited in extent. Surgical debulking can be used to achieve biochemical control, improve response to systemic therapies with diminished tumor burden, and palliate symptoms. However, when extra-abdominal disease is present, a sustained biochemical response is unlikely after resection, stressing the importance of patient selection and determination of treatment goals preoperatively. Palliative therapy may include treatment with alpha-methyltyrosine, which inhibits catecholamine synthesis, as well as alpha- and beta-blockades. Somatostatin analogs have also been used for symptomatic relief. The most commonly used systemic chemotherapy regimens for pheochromocytoma are high-dose streptozocin and a combination of cyclophosphamide, vincristine, and dacarbazine. The overall response rates with these regimens are approximately 50%. Radiation therapy has been effective only for symptomatic relief of bony metastases. There has been some interest in treating metastatic lesions with therapeutic doses of ^{131}I-MIBG. Unfortunately, a high percentage of metastatic pheochromocytomas do not take up ^{131}I-MIBG; therefore, the symptom response rate is 75% to 90% while the tumor response rate is

30% to 47%. Other alternative options for the treatment of metastatic disease include arterial embolization, chemoembolization, cryoablation, and radiofrequency ablation. The 5-year survival rate for patients with malignant pheochromocytoma is approximately 43%, with no significant difference in survival between adrenal and extra-adrenal pheochromocytomas. Patients with benign pheochromocytoma have a 97% 5-year survival rate.

Pheochromocytoma in pregnancy deserves special mention. Pheochromocytoma occurs in 1 among 50,000 pregnancies. Historically, maternal and fetal mortality was approximately 50%; however, with improvements in detection and treatment, mortality rates have decreased to 5% and 15%, respectively. Plasma and urine metanephrines should be used for screening. MRI is the preferred imaging modality during pregnancy rather than CT or MIBG. Surgical resection of a pheochromocytoma is recommended during the first or second trimester, while those that are diagnosed during the third trimester can be resected after delivery. Cesarean delivery is recommended due to the decreased risk of maternal mortality compared to a vaginal delivery in the setting of an in situ pheochromocytoma. Prior to delivery, preoperative alpha and beta blockade should be used. Of note, phenoxybenzamine poses a risk of hypotension and respiratory depression in the newborn during the first 48 hours of life. Genetic testing is indicated in these patients, as 30% of pregnant women with a pheochromocytoma have a hereditary syndrome.

ADRENAL CORTICAL CARCINOMA

Introduction

Adrenal cortical carcinoma is a rare endocrine malignancy with an incidence of 0.5 to 2 cases per 1 million people each year in the United States. There is a bimodal age distribution, with incidence peaking in young children less than 5 years old and then again between 40 and 50 years of age. Prognosis tends to be poor because the diagnosis is usually delayed, with one-third of patients presenting with metastatic disease, and there is a dearth of effective systemic chemotherapy options. Surgical resection remains the mainstay of curative therapy. Even after surgical resection, rates of locoregional recurrence and metastasis are as high as 85%. Five-year survival rates range from 16% to 50%.

Advances in molecular biology have identified several genetic

alterations associated with adrenal cortical carcinoma. In particular, the two most common mutations found in adrenal cortical carcinoma are the overexpression of IGF-2, occurring in nearly 90% of cases, and over-activation of the Wnt/β-catenin pathway. The presence of β-catenin nuclear staining is associated with worse overall survival in patients with adrenal cortical carcinoma. Mutations in the tumor suppressor gene TP53 are seen in 60% to 80% of pediatric adrenal cortical carcinomas but in only 4% of adult cases. Sporadic mutations of TP53 are associated with a poor prognosis. Ki-67 has been demonstrated to be a prognostic marker and may be useful in treatment planning.

Clinical Manifestations

Patients with adrenal cortical carcinoma usually present with vague abdominal symptoms secondary to an enlarging retroperitoneal mass or with clinical manifestations of overproduction of one or more adrenal cortical hormones. Most of these tumors (>80%) are functional as measured by biochemical parameters. Up to 50% secrete cortisol, producing Cushing syndrome. The workup and treatment of patients with Cushing syndrome have been described above. Another 10% to 20% of adrenal cortical carcinomas produce androgens, estrogens, or aldosterone, which can cause virilization in females, feminization in males, or hypertension, respectively.

Diagnosis

The preoperative evaluation of these patients involves biochemical screening for hormone overproduction as detailed above. With a cortisol-secreting tumor, the results of these tests serve to guide perioperative glucocorticoid replacement therapy. Screening to exclude pheochromocytoma should also be performed. Standard preoperative staging in patients with suspected adrenal cancer includes high-resolution abdominal CT or MRI. MRI may be especially helpful in delineating tumor extension into the inferior vena cava. Positron emission tomography when combined with CT imaging may be helpful in detecting metastasis or recurrence in patients with adrenal cortical cancer. Chest radiography is used to rule out pulmonary metastasis. The median size of these tumors is 11 cm. Preoperative biopsy is not typically recommended (see discussion in Adrenal Incidentaloma section). The two most commonly used staging

systems for adrenal cortical carcinomas are shown in Table 16.6.

TABLE 16.6 Major Staging Systems for Adrenal Cortical Carcinoma

Stage	American Joint Committee on Cancer 7th Edition (AJCC)/International Union against Cancer, 7th Edition (UICC)	European Network for the Study of Adrenal Tumors (ENSAT)
I	T1 (≤5 cm, without extra-adrenal invasion), N0, M0	T1 (≤5 cm, without extra-adrenal invasion), N0, M0
II	T2 (>5 cm, without extra-adrenal invasion), N0, M0	T2 (>5 cm, without extra-adrenal invasion), N0, M0
III	T1/T2, N1, M0 T3 (extra-adrenal invasion, but not invading adjacent organs), N0, M0	T3 (extra-adrenal invasion), N0, M0 T4 (invasion of adjacent organs), N0, M0 Any T, N1, M0
IV	T3, N1, M0 T4 (invasion of adjacent organs), N0/N1, M0 Any T, Any N, M1 (distant metastasis)	Any T, Any N, M1

Treatment

Complete surgical resection is currently the only potentially curative therapy for localized adrenal cortical cancer. Approximately 50% of the tumors are localized to the adrenal gland at the time of initial presentation.

Several studies have examined the issue of laparoscopic versus open resection for adrenal cortical carcinoma. Donatini et al. propose that laparoscopic resection for stage I and II tumors (≤10 cm with no extra-adrenal invasion) can be performed without compromising oncologic outcomes. However, several other centers, including our own, have reported that laparoscopic resection is associated with higher rates of local and peritoneal recurrence, positive margins, shorter time to recurrence, and worse overall survival compared to open resection. These results are likely due to high rates of tumor fracture and peritoneal contamination of the typically soft adrenal cancers during the laparoscopic procedure, despite the procedure apparently appearing technically feasible to the operating surgeon based on preoperative imaging assessment. For this reason, we continue to prefer open adrenalectomy for patients with known or suspected adrenal cortical carcinoma. An open transabdominal approach

facilitates adequate exposure to ensure complete resection, minimizes the risk of tumor spillage, and allows for vascular control of the inferior vena cava, aorta, and renal vessels when necessary. Radical en bloc resection of adrenal cortical carcinoma that includes adjacent organs, if involved by tumor, provides the only chance for long-term survival, and should be performed when possible. Routine nephrectomy or resection of other adjacent organs, however, without radiographic or macroscopic evidence of invasion, is generally not warranted. Tumor thrombectomy of the renal vein or inferior vena cava may be required. Lymph node invasion is common in patients with adrenal cortical carcinoma and is associated with worse overall survival. Patients who undergo lymphadenectomy have been reported to have improved survival and recurrence rates, and therefore, lymphadenectomy of radiographically or clinically suspicious lymph nodes should be performed at the time of adrenalectomy, and formal lymph node dissection (potentially including celiac, renal hilum, and ipsilateral aortic lymph nodes) should be at least selectively considered.

Risk factors for local recurrence include the center at which surgery is performed (tertiary referral center vs. other), age, stage at presentation, and incomplete resection. Patients who undergo a complete resection of their tumor have a 5-year survival rate of approximately 40% and a median survival of 43 months; those who undergo incomplete resection have a median survival less than 12 months. Therefore, the strongest predictor of outcome in this disease is the ability to perform a complete resection. The importance of complete resection has been highlighted in a study of 113 patients treated for adrenal cortical cancer at Memorial Sloan–Kettering Cancer Center. Patients with complete primary resections had improved 5-year survival rates compared to patients with incomplete resections (55% vs. 5%). Moreover, the benefit of complete resection was demonstrated in selected patients who underwent repeat surgery. Patients with a complete second resection demonstrated improved 5-year survival rates compared to patients with an incomplete second resection (57% vs. 0%).

Common sites of metastasis of adrenal cortical carcinoma include lungs, lymph nodes, liver, peritoneum, and bone. Complete resection of recurrent disease, including pulmonary metastases, is associated with prolonged survival in select patients and can help control symptoms related to excess hormone production. Surveillance after surgical resection for adrenal cortical carcinoma is typically by CT or MRI of the abdomen and CT of the chest, in addition to biochemical testing, every 3 to 4 months. After 2

years of follow-up, the frequency of surveillance may be decreased, but should continue for at least 10 years.

Mitotane has been one of the most commonly used systemic agents in patients with advanced adrenal cortical carcinoma. This drug is an isomer of dichlorodiphenyltrichloroethane (DDT) and not only inhibits steroid production but also leads to atrophy of adrenal cortical cells. Mitotane is associated with a number of side effects, most notably gastrointestinal and neuromuscular symptoms. In addition, the drug has a relatively narrow therapeutic range (ideal plasma level >14 to 20 mg/L), and it requires close monitoring of serum levels to minimize toxicity as well as provision of exogenous steroid hormone replacement to avoid symptoms associated with adrenal insufficiency due to suppression of cortisol production by the normal contralateral gland. The role of mitotane in the adjuvant setting after radical resection of adrenal cortical carcinoma remains controversial. A 2007 nonrandomized retrospective study by Terzolo et al. examined the role of adjuvant mitotane postoperatively with respect to overall and recurrence-free survival. The authors examined 177 patients with adrenal cortical carcinoma who had undergone resection in 55 centers in Italy and Germany over a period of 20 years. The study included a group of 47 Italian patients treated at a single center with adjuvant mitotane and compared these patients to a group of 55 Italian patients as well as another group of 75 German patients who had not received adjuvant mitotane. While there was no significant difference in overall survival, recurrence-free survival was prolonged in the mitotane group (median 42 months) compared to the Italian (10 months) and German (25 months) controls. The recurrence rates were 49% in the mitotane group, 91% in the Italian control group, and 73% in the German control group. Limitations of the study included lack of details regarding the mitotane regimen and potential inconsistencies in surgery and follow-up evaluation among the various institutions over the span of two decades, resulting in an ascertainment or lead-time bias in the detection of recurrences. Importantly, the high recurrence rate of the Italian control group suggests that some patients may not have had a complete resection.

Our group has examined 218 patients with adrenal cortical carcinoma who underwent primary resection either at our MD Anderson Cancer Center institution (28 patients) or an outside institution (190 patients). After a median follow-up of 7.3 years, patients who had undergone surgery at MD Anderson had superior overall survival compared with

outside patients (median not reached vs. 44 months) as well as superior disease-free survival (median of 25 months vs. 12 months). The overall survival rates were 68% versus 32%, and the recurrence rates were 50% versus 86% for the MD Anderson and outside patients, respectively. Twenty-two of the 218 patients (10%) in this series received adjuvant mitotane. A subsetanalysis demonstrated a prolonged disease-free survival in the mitotane group (median of 30 months vs. 12 months) without a benefit in overall survival. Importantly, the outcomes of the index and outside patient groups in our study compare favorably to the outcomes of the mitotane and control groups in the Terzolo et al. study. Based on these results, differences in outcomes between the patient groups in the European mitotane study may be related at least in part to quality and completeness of surgery rather than adjuvant mitotane therapy. We and others therefore have advocated individualizing adjuvant mitotane therapy in the postoperative management of patients with resected adrenal cortical carcinoma; we generally favor adjuvant mitotane in the postoperative management of relatively young healthy patients with a good performance status.

The US Adrenocortical Carcinoma Group examined the outcomes of 207 patients who received adjuvant mitotane after surgical resection. After adjusting for tumor factors, the receipt of mitotane was not associated with improved recurrence-free or overall survival. The Efficacy of Adjuvant Mitotane Treatment (ADIUVO) trial is currently underway and will give us some additional insight into the utility of adjuvant mitotane. Until then, Kim et al. have created a nomogram to accurately predict recurrence and survival after resection of adrenal cortical carcinoma; variables included are tumor size, nodal status, T stage, cortisol secretion, capsular invasion, and resection margins. This nomogram can help select high-risk patients who may be candidates for adjuvant therapy following resection of adrenal cortical carcinoma.

While no chemotherapeutic agent or combination of agents has been shown to be consistently effective against unresectable or metastatic adrenal cortical cancer, the FIRM-ACT trial has established combination chemotherapy with mitotane as the standard of care for patients with unresectable adrenal cortical carcinoma. This study randomized 304 patients to receive etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) or streptozocin and mitotane (Sz-M). Response rates were higher with EDP-M compared to Sz-M (23.2% vs. 9.2%, $P < 0.001$), and median time

to progression with EDP-M was longer (5.0 months vs. 2.1 months; hazard ratio 0.55; 95% confidence interval, 0.43 to 0.69; $P < 0.001$). The median survival of the EDP-M group was 14.8 months versus 12 months for patients in the Sz-M group, which was not statistically significant (hazard ratio 0.79; 95% confidence interval, 0.61 to 1.02; $P = 0.07$), emphasizing the need for improved systemic therapies for patients with adrenal cortical carcinoma.

The potential role of radiation therapy as adjuvant treatment following primary resection for adrenal cortical carcinoma remains controversial; it is more commonly used selectively (delivered via external beam or as brachytherapy) following resection for locoregional recurrence. Radiation therapy has an established role for treatment of isolated metastasis from adrenal cortical carcinoma, including as palliative therapy for bone metastasis.

Our group has examined the use of preoperative chemotherapy in patients with borderline resectable adrenal cortical carcinoma. Fifteen patients evaluated between 1995 and 2012 were deemed borderline resectable for one of three reasons: perceived requirement of multivisceral or vascular resection with high associated risk for a margin-positive resection; radiographic suspicion of metastatic disease or potentially resectable confirmed oligometastatic disease; or patient condition or comorbidities not amenable to an extensive surgical procedure. Based on standard RECIST criteria, 38% of evaluable patients had a partial response to neoadjuvant therapy, and six of seven patients with a vena caval tumor thrombus experienced at least a 30% reduction in the extent of the tumor thrombus. Eighty-seven percent of patients (13 of 15) were able to undergo surgical resection, with a 92.3% negative margin rate (R0). Median disease-free survival was 27.6 months for patients who underwent neoadjuvant chemotherapy compared to 12.6 months for patients with adrenal cortical carcinoma who underwent upfront surgery ($P = 0.48$), while actuarial 5-year overall survival was 65% and 57%, respectively. Based on this early experience, neoadjuvant chemotherapy may be an attractive option for selected patients with borderline resectable adrenal cortical carcinoma who are considered good candidates for initial chemotherapy followed by surgery.

ADRENAL INCIDENTALOMA

With the widespread use of abdominal CT imaging, asymptomatic and

unanticipated adrenal lesions are discovered with increasing frequency. These lesions, termed incidentalomas, are seen in up to 5% of routinely performed abdominal imaging studies and in up to 9% of autopsy series. Incidentalomas are more commonly found in white, obese, diabetic, hypertensive, and elderly patients, and are rare in children and adolescents. Although most of these lesions represent benign adenomas, some are hormonally active, and only a small minority represents an invasive malignancy. The risk of an incidentaloma being associated with hypercortisolism is approximately 5%, a pheochromocytoma 3% to 5%, aldosteronism 1%, adrenal cortical carcinoma 2% to 5%, and metastasis to the adrenal gland 2.5%. In contrast, in patients with a known extra-adrenal malignancy with biologic behavior that includes adrenal metastasis (e.g., lung cancer, melanoma, renal cell carcinoma), up to 50% to 75% of adrenal tumors are metastases. Fifteen percent of adrenal incidentalomas will be bilateral.

The European Society of Endocrinology Clinical Practice Guideline states that patients identified with an incidental adrenal mass >1 cm in size should be screened to rule out a hormonally active adenoma or pheochromocytoma. Evaluation of patients with an incidentally identified adrenal mass includes measurement of serum electrolyte levels, an overnight 1-mg dexamethasone suppression test (described previously), and measurement of plasma metanephrine levels. Patients with hypertension and an adrenal incidentaloma should also have plasma aldosterone and renin levels drawn in order to calculate the plasma aldosterone: renin ratio. DHEAS may be helpful in evaluating for subclinical Cushing syndrome, but levels of other sex hormones and steroid precursors are not routinely checked unless the patient is found to have symptoms of hormone excess (hirsutism, virilization) or if imaging findings are suspicious for adrenal cortical carcinoma. In general, any hormonally active lesion, regardless of size, should be resected. Furthermore, surgery is indicated if the adrenal mass demonstrates radiographic characteristics suggestive of malignancy or if the tumor enlarges during follow-up. Fine-needle aspiration biopsy is rarely indicated in the evaluation of an adrenal incidentaloma. If percutaneous biopsy is felt to be indicated (e.g., to assist with treatment planning in a patient with known or suspected metastatic cancer), a diagnosis of pheochromocytoma should be excluded prior to performing the biopsy to avoid inducing paroxysmal hypertension.

If the incidentaloma is nonfunctioning, the risk of malignancy is related to its size and radiographic characteristics. CT is ideal for the characterization of adrenal incidentalomas. A benign adrenal adenoma typically has high lipid content, resulting in low attenuation on CT (≤10 HU). Adenomas also demonstrate rapid washout of contrast medium on adrenal protocol CT compared to pheochromocytomas, carcinomas, or adrenal metastases. Adrenal adenomas on MRI lose signal on out-of-phase images in relation to the spleen. However, it is important to recognize that up to 30% of benign adenomas do not contain high levels of lipid, making MRI and CT less useful in the diagnosis.

Size remains the single best clinical indicator of primary malignancy in patients who present with an incidental adrenal mass. Adrenal cortical carcinoma accounts for 2% of tumors less than 4 cm in size compared to 25% or more of tumors more than 6 cm in size. In addition, 90% of adrenal cortical carcinomas are larger than 6 cm. In general, lesions larger than 6 cm should be resected because of the relatively high risk of malignancy. Data from our own institution and elsewhere have identified rare patients with adrenal cortical carcinomas arising in tumors smaller than 5 cm. The overwhelming majority of these small tumors had CT or MRI characteristics suspicious for carcinoma such as heterogeneity and irregular borders. Recent recommendations for resection of nonfunctioning adrenal masses have ranged from 5 cm down to 3 cm. A cost-effectiveness analysis by Wang et al. supports the American Association of Clinical Endocrinologists (AACE) and American Association of Endocrine Surgeons (AAES) recommendation that tumors ≥4 cm be resected. The recent success and advantages of laparoscopic adrenalectomy have led some investigators to suggest operative removal of even relatively small incidentalomas. However, the decision to operate on a nonfunctioning adrenal incidentaloma must also take into account the patient's comorbidities, life expectancy, and personal wishes.

At MD Anderson, we recommend adrenalectomy for all biochemically confirmed functioning adrenal tumors and those with suspicious radiographic findings regardless of size. Nonfunctioning tumors between 3 and 6 cm in diameter are most appropriately managed on an individual basis, taking into consideration patient age and comorbidities. For example, a 3-cm tumor in an otherwise healthy 40-year-old patient is probably most appropriately managed by adrenalectomy, whereas the same tumor in a 75-year-old patient with multiple comorbidities might be

observed. Figure 16.3 provides an overview of our approach to patients with adrenal incidentalomas.

Small, hormonally inactive adrenal incidentalomas can be observed. In this scenario, the NIH Consensus statement and AACE/AAES guidelines recommend repeat imaging at 6, 12, and 24 months. Biochemical testing is recommended annually for 4 to 5 years. If the mass enlarges by more than 20% in largest diameter or becomes hormonally active, consideration for resection is recommended. In patients whose tumors remain stable in size and biologically nonfunctioning, no further follow-up is recommended after 5 years. Table 16.7 outlines a variety of recommended regimens for the radiographic surveillance of an adrenal incidentaloma.

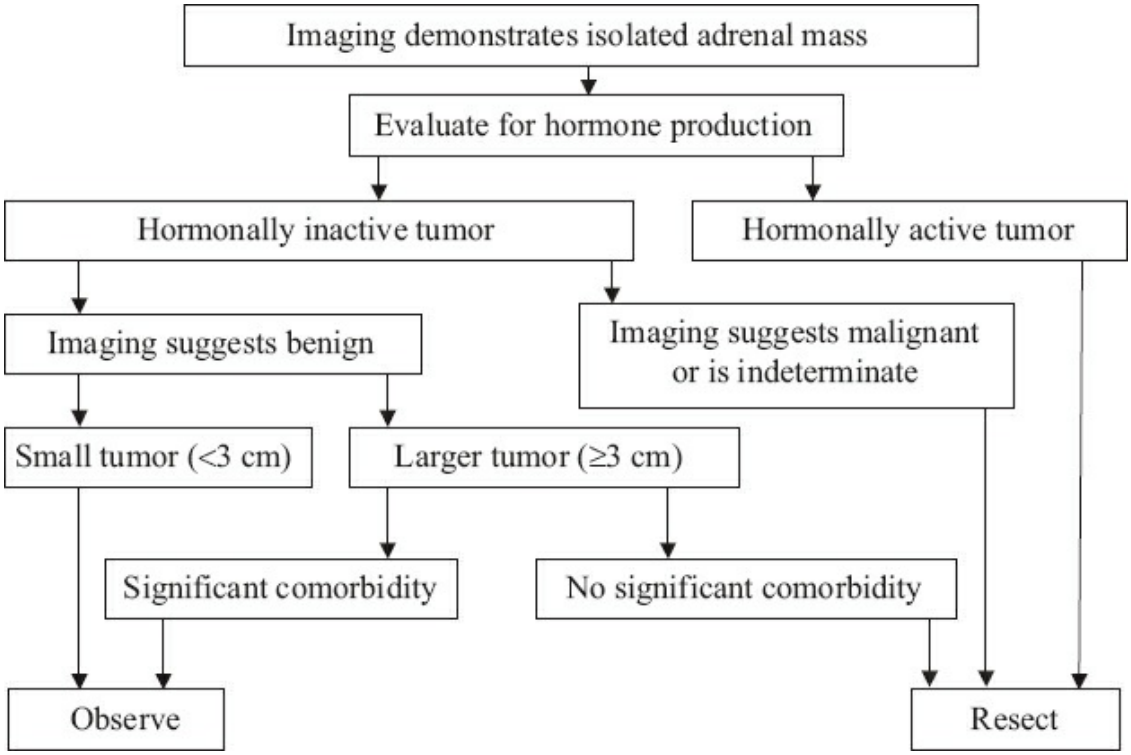

Figure 16.3 An algorithm for the evaluation of patients with isolated, incidentally identified adrenal tumors.

ADRENAL METASTASES

Cancer metastasis to the adrenal glands is relatively common, occurring in up to 27% of patients with extra-adrenal malignancies at autopsy. Based on these studies, 42% of lung cancers, 16% of gastric cancers, 58% of breast cancers, 50% of malignant melanomas, and a high percentage of renal and prostate cancers have metastasized to the adrenal glands by the time of death. The adrenal gland is the sole site of metastatic disease in

75% to 85% of patients, and the majority present with metachronous disease (>6 months after diagnosis of the primary malignancy). Most patients are asymptomatic from the standpoint of their adrenal metastasis, and adrenal insufficiency is encountered only occasionally (e.g., bilateral adrenal metastases from lung cancer). In general, more than 90% of normal adrenal cortical tissue in both adrenal glands must be replaced before clinically detectable adrenal cortical hypofunction is appreciated. When adrenal insufficiency does occur, it is usually in the setting of gross bilateral enlargement of the adrenal glands as detected by CT. Bilateral adrenal metastases occur in 4% of patients.

Evaluation of the patient with an adrenal mass and a history of malignancy includes an evaluation for hormone production, since as many as 50% of these patients will have occult, functioning adrenal tumors unrelated to their prior malignancy, for example, pheochromocytoma (Fig. 16.4). Functional assessment for hormone overproduction is similar to patients without malignancy and found to have an incidentaloma, and should include an overnight 1-mg dexamethasone suppression test, plasma metanephrines, and plasma renin and aldosterone levels in hypertensive patients. As mentioned earlier, CT is the preferred imaging modality for an incidentaloma, as benign adenomas have low attenuation on noncontrast CT and rapid washout on contrast CT images. PET/CT is more frequently used in patients with a known malignancy, and can be used to help differentiate between benign and malignant adrenal lesions. Adrenal adenomas are usually not FDG-avid, while malignant lesions are FDG-avid, although PET/CT has a false-positive rate of 20% in detecting malignancy.

TABLE **16.7** Examples of Recommended Follow-Up Regimens for a Patient with a Nonfunctioning, Benign-Appearing Adrenal Incidentaloma

Author, Publication	Who to Image	How to Image	When to Image
European Society of Endocrinology Clinical Practice Guidelines/European Network for the Study of Adrenal Tumors, 2016	Benign-appearing, <4 cm Indeterminate-appearing	No routine imaging Noncontrast CT or MRI	No routine imaging 6–12 months after diagnosis
Italian Association of Clinical Endocrinologists (AME) Position Statement, 2011	Benign-appearing	CT	3–6 months after diagnosis, once
Boland, AJR, 2011	Benign-appearing	CT	6 months after diagnosis, then no further imaging if stable
White Paper of the ACR, 2010	<4 cm	Noncontrast CT Or MRI	12 months after diagnosis
AACE/AAES Guidelines, 2009	Benign-appearing, <4 cm	Noncontrast CT Or MRI	3–6 months after diagnosis, then annually for 1–2 years
Young, NEJM 2007	<4 cm	CT	6, 12, and 24 months after diagnosis, then consider no further imaging if stable
NIH Consensus, 2002	Benign-appearing, <4 cm	CT	6–12 months after diagnosis, then consider no further imaging if stable

Fine-needle aspiration biopsy may be helpful in selected patients with suspected adrenal metastasis when the results would influence the treatment plan; for example, to confirm the diagnosis of metastasis in those who are not surgical candidates. Percutaneous biopsy can be done under CT or ultrasound guidance, and has been shown to be 89% sensitive in the diagnosis of malignancy. A nondiagnostic sample is obtained in 5% of cases. Complication rates of adrenal biopsy range from 3% to 13%, with the most common complications being adrenal hematoma, abdominal pain, pancreatitis, hematuria, pneumothorax, abscess, and tumor seeding of the biopsy tract. Percutaneous biopsy should not be performed in patients suspected of having primary adrenal cortical carcinoma when the initial

treatment plan would be surgery, and pheochromocytoma should always be excluded by biochemical testing prior to biopsy. In selected patients, surgical treatment of a suspected adrenal metastasis may be planned solely based on the patient's history and on noninvasive studies without preoperative needle biopsy. A history of a malignancy that commonly metastasizes to the adrenal glands, with favorable tumor biology, negative biochemical screening for hormone production, and a mass that either fulfills size criteria for surgical excision or is radiographically suspicious for metastasis, may be considered for resection without preoperative tissue diagnosis.

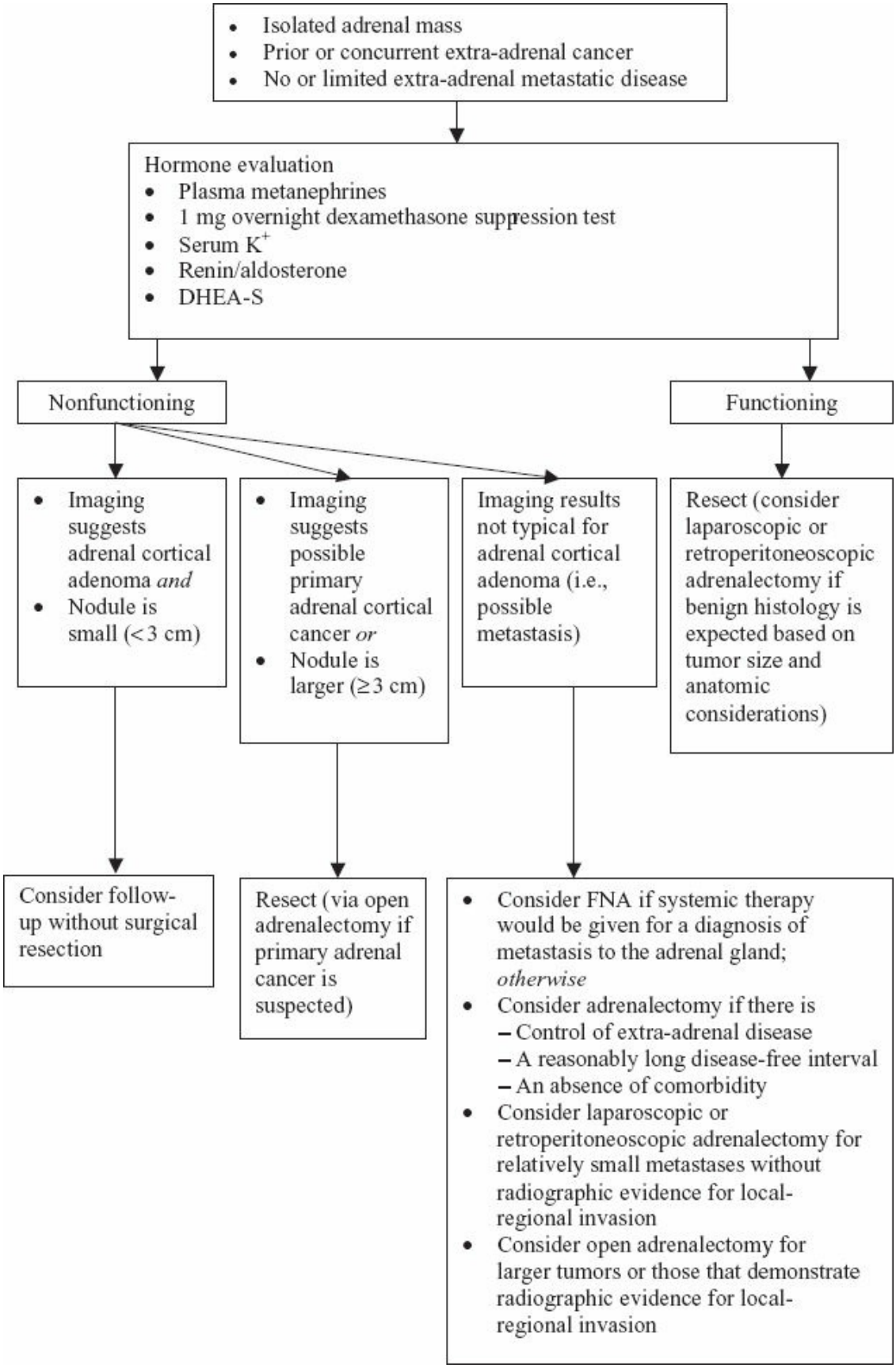

Figure 16.4 An algorithm for the evaluation and surgical treatment of patients with extra-adrenal cancer presenting with an adrenal mass. VMA, vanillylmandelic acid.

Surgery for isolated metastases to the adrenal gland can be considered in highly selected patients. Appropriate selection criteria include good-risk individuals in whom there is a prolonged disease-free interval and evidence of favorable underlying tumor biology. Favorable tumor biology is implied in those who have had a significant progression-free interval, those who have responded to systemic therapy, and those who have a history of isolated metachronous metastases. Primary tumor site also appears to affect survival, in that longer median survival times are observed following resection of metastases from primary renal, melanoma, colon, and lung cancers, and poorer survival in patients with esophageal, liver, unknown primary tumors, and high-grade sarcomas. Metachronous disease, disease-free interval of >12 months, complete resection of the adrenal metastasis (R0 vs. R1/R2), and smaller tumor size are associated with prolonged survival after adrenal metastasectomy. Several studies have shown that open and laparoscopic adrenalectomy for metastasis are feasible and have equivalent rates of positive margins, local recurrence, and overall survival, as long as sound judgment is used in determining the safest approach for each patient based on tumor characteristics and surgeon experience.

SURGICAL APPROACH

Introduction

When choosing an operative approach for a patient with an adrenal tumor, several factors must be considered: the size and site of the tumor, the malignant potential of the disease, the laterality or bilaterality of the disease, the presence of multiple or extra-adrenal tumors, the presence of additional intra-abdominal disease or extra-abdominal extension, history of prior abdominal surgery, the patient's body habitus, and the surgeon's experience. As a general rule, large tumors and tumors suspected to represent a primary malignancy are best approached with an open operation.

Open Adrenalectomy

An open adrenalectomy is indicated for known or suspected primary adrenal cancer, large tumors, recurrent disease, and for tumors that involve adjacent viscera. Open adrenalectomy can be performed by four

approaches: anterior, posterior, lateral (flank), and thoracoabdominal.

The anterior approach is the preferred method for resection of most adrenal cortical carcinomas. The patient is placed in a supine or semi-lateral position. Access is accomplished via a midline incision, a bilateral subcostal incision, or a Makuuchi (hockey stick-shaped) incision. For an open left adrenalectomy, the splenic flexure and descending colon are mobilized inferiorly and the retroperitoneum is entered by incising along the inferior border of the pancreas. Medial visceral rotation of the spleen and tail of the pancreas is usually helpful and necessary when dealing with large tumors. The adrenal gland can be visualized by exposing the renal hilum and then following the left renal vein to the junction of the adrenal vein. The left adrenal gland lies lateral to the aorta, just above the left renal vein. The adrenal vein can be ligated early in the procedure to limit the release of catecholamines when dealing with a pheochromocytoma; it should be recognized, however, that early venous ligation may increase venous congestion and bleeding from the tumor. Small arterial perforators from the aorta, inferior phrenic, and renal arteries are identified and ligated with sutures or with energy alone. Open adrenalectomy of the right adrenal gland is approached similarly; on the right side, mobilization of the right triangular ligament of the liver allows anteromedial rotation of the liver and access to the right adrenal gland. A Kocher maneuver facilitates exposure of the right kidney and vena cava and is helpful when the adrenal tumor is large. The right adrenal vein generally drains directly into the vena cava and is very short. Care is taken to control it appropriately with suture ligation or a vascular stapler. Drains are used selectively but are usually unnecessary, especially in the absence of multiorgan resection.

The open posterior approach, formerly commonly used in the resection of small, benign adrenal tumors (e.g., aldosteronomas), is now rarely employed. The procedure begins with the patient in a prone position with the table flexed about 35 degrees. An oblique incision is made over the 12th rib with retraction of sacrospinalis muscle medially, resection of the 12th rib, and reflection of the pleura superiorly. On the left, the superior extent of the dissection is the diaphragm. The perirenal fat and soft tissues are reflected downward with the diaphragm exposed superomedially. Medially, a vertically coursing inferior phrenic vein can be encountered indicating the adrenal gland is nearby, laterally. On the right, care is taken to preserve the subcostal nerve and exposure is facilitated by transecting the free edge of the diaphragm medially to the spine. The adrenal gland is

located against the bare area of the liver with exposure of the liver delineating the superior extent of the dissection.

In the lateral (flank) approach, the patient is placed in a lateral decubitus position with an extraperitoneal approach to the involved side. The lateral approach can be helpful in obese patients with gravity assisting the retraction. The lateral approach, like the posterior approach, can obviate the need to perform extensive adhesiolysis in a patient with previous abdominal surgery. However, vascular control of large vessels may be difficult.

The thoracoabdominal approach provides the broadest exposure and is occasionally useful for tumors that may require en bloc resection of adjacent organs or extensive lymph node dissection. The patient is placed in the decubitus position and the incision is carried over the 10th rib on the right or over the 11th rib on the left, followed by resection of the rib. For tumors with significant extension into the IVC, the hepatic veins, or the right atrium, a median sternotomy may be necessary.

Laparoscopic Adrenalectomy

Since the first description of laparoscopic adrenalectomy in 1992, this approach has been expanded and is considered now the standard approach for modestly sized benign adrenal tumors as well as selected metastases to the adrenal gland. Patients who undergo laparoscopic adrenalectomy have a more rapid recovery, less discomfort, faster return to preoperative activity level, and better cosmetic results compared to patients who undergo open adrenalectomy.

Patients who are good candidates for laparoscopic adrenalectomy include those with aldosterone-producing adenomas; other small (<4 cm) functioning or nonfunctioning but presumably benign cortical neoplasms; those with unilateral, benign-appearing sporadic pheochromocytomas; MEN II or von Hippel–Lindau syndrome patients with a unilateral pheochromocytoma; and selected patients with adrenal metastasis. Bilateral laparoscopic adrenalectomy can be performed in selected patients with bilateral adrenal hyperplasia. Laparoscopic cortical-sparing partial adrenalectomy has been successfully performed in patients with bilateral pheochromocytomas in the familial setting. We continue to urge caution in the use of laparoscopic adrenalectomy for patients with malignant or potentially malignant primary adrenal tumors. This includes the occasional patient with cortical neoplasms (functioning or nonfunctioning) 4 cm in

size or greater with radiographic features suggesting malignancy.

For a standard, 4-port transperitoneal laparoscopic left adrenalectomy, the patient is placed in the right lateral decubitus position, with the table appropriately padded and flexed. The abdomen and chest are prepped from the nipple to below the iliac crest, and from the right of the umbilicus to the vertebral column. An infracostal 12-mm port, 10 to 15 cm anterior to the anterior axillary line, is placed using the open technique, abdominal insufflation achieved, and the 30-degree laparoscope is inserted. Three additional trocars are then placed under direct vision. One is placed at the anterior axillary line (12 mm), one is placed at the posterior axillary line (5 mm), and one is placed 5 cm posterior to the posterior axillary port, just medial to the left kidney (5 mm). Dissection begins by mobilizing the splenic flexure of the colon, and gravity is used to carry it inferiorly and medially. Mobilization of the spleen is performed by incising the peritoneum lateral to the spleen. This incision is developed around to the level of the short gastric vessels. This allows the spleen to rotate medially. It is often helpful to move the laparoscope to the posterior port as dissection proceeds to maximize visualization of the adrenal bed. The adrenal gland is dissected from the retroperitoneal fat; the Harmonic Scalpel (Ethicon Endo-Surgery, Inc.) works well for this dissection. In contrast to the open approach, technical considerations in laparoscopic adrenalectomy often result in delaying ligation of the adrenal vein to the penultimate step in the procedure, following complete mobilization of the tumor and the adrenal gland, and just prior to specimen removal. Vein division on the left side can be safely accomplished with either the vascular stapler or with two titanium clips placed on the proximal side of the vein. The specimen is removed in a sterile plastic retrieval bag through the umbilical port site. Laparoscopic right adrenalectomy is performed with similar positioning in the left lateral decubitus position. Abdominal access is obtained through placement of four ports, placed similar to those on the left side. The most medial port is used to assist in retraction of the liver. The surgeon begins the operation through the two lateral ports; the right lateral hepatic attachments and the right triangular ligament of the liver are divided to allow for medial retraction of the liver. The adrenal gland is then dissected inferiorly along the renal vein and medially along the vena cava. The right adrenal vein is usually short and wide, and drains directly into the vena cava. Again, either the vascular stapler or titanium clips may be used to secure the vein on the right side.

Posterior Retroperitoneoscopic Adrenalectomy

The posterior retroperitoneoscopic adrenalectomy (PRA) has become the preferred technique at our institution for resection of small, benign adrenal masses and isolated metastases to the adrenal gland. The technique of PRA was first reported by Mercan et al. in 1995 and further modified by Walz et al. in Essen, Germany. This method offers the advantage of a minimally invasive approach to the adrenal glands, obviating the need for adhesiolysis while minimizing hemodynamic or respiratory instability from CO_2 insufflation. In addition, this approach allows the surgeon to address bilateral disease without the need for patient repositioning. Contraindications include suspicion of adrenal cortical carcinoma, adjacent organ invasion, lesions greater than approximately 6 cm, morbid obesity, and limited distance between the ribs and iliac crest. Barczyn´ski et al. performed a randomized clinical trial comparing PRA and lateral transperitoneal laparoscopic adrenalectomy for adrenal lesions less than 7 cm in size. In this investigation, PRA was associated with decreased operative time and blood loss, decreased postoperative pain and nausea, improved time to ambulation, shorter length of stay and lower hospital costs. In contrast, a meta-analysis by Nigri et al. did not show any differences in these same outcomes between PRA and laparoscopic adrenalectomy. Thus surgeon experience and preference can continue to dictate the technical approach to minimally invasive adrenalectomy in most situations.

With the patient placed in a prone jackknife position on a Cloward table saddle (Fig. 16.5), the 12th rib is palpated and a 1.5-cm transverse incision is made just beneath the tip of the rib. This will be the eventual site of the middle (12 mm) trocar. The soft tissues are divided sharply and the retroperitoneal space is entered. Using the index finger, a small space is created, and the index finger is then used to guide the placement of the medial (12 mm) and lateral (5 mm) trocars into this space. The medial trocar is placed approximately 5 cm medial to the middle trocar site, just lateral to the paraspinal musculature. This trocar is angled at 45 degrees and aimed slightly laterally toward the adrenal gland. The lateral trocar is placed approximately 5 cm lateral to the middle trocar site, beneath the 11th rib, and aimed medially. A blunt 12-mm trocar with an inflatable balloon and an adjustable sleeve is then placed into the retroperitoneal space through the middle incision. Pneumoretroperitoneum is then created with CO_2 insufflation to a pressure of up to 24 mm Hg.

Figure 16.5 Patient positioning for a right-sided posterior retroperitoneoscopic adrenalectomy.

A 30-degree 10-mm videoscope is first inserted through the middle trocar, allowing for a combination of blunt and sharp dissection to establish the retroperitoneal space beneath the diaphragm. The videoscope can then be switched to the medial trocar, and the middle and lateral trocars used as the working ports. Gerota's fascia is entered and the superior pole of the kidney is identified. The psoas muscle, the posterior surface of the liver or spleen which is visible through the peritoneum, and the superior pole of the kidney serve as landmarks. On the right side, the inferior vena cava is a key landmark.

The adrenal gland is allowed to retract superiorly with gentle downward retraction on the kidney. Division of the tissue along the superior border of the kidney is performed using the Harmonic Scalpel, the EnSeal device (Ethicon Endo-Surgery, Inc.), or laparoscopic scissors. It is important to dissect the adrenal gland from the kidney before dividing the superior and medial attachments of the gland. This maneuver minimizes direct manipulation of the fragile adrenal gland and allows the gland to be suspended from its superior attachments until late in the procedure, greatly facilitating dissection.

On the left side, the adrenal vein drains inferiorly into the renal vein. On

the right side, the adrenal vein is identified coursing medially to drain into the inferior vena cava. The inferior vena cava must be carefully identified. Due to high insufflation pressures, it loses its normal tubular appearance and its lateral border appears as a flat white line. The adrenal vein is dissected and divided between clips, while simultaneously retracting the gland on the distal side of the adrenal vein. Bleeding tends to be very modest due in part to the high insufflation pressures.

The adrenal gland is then completely mobilized medially and superiorly. A retrieval bag is used to remove the specimen through the middle trocar site. The retroperitoneal space is then inspected for hemostasis. Insufflation is gradually decreased to pressures of 8 to 12 mm Hg, facilitating visualization of any venous bleeding that may have been tamponaded by the high insufflation pressures. Ports are then removed, and the skin is closed with absorbable suture.

We have updated and published our experience with PRAs performed at MD Anderson between 2005 and 2010. One hundred and eighteen PRAs were performed for indications which included functioning tumors (pheochromocytomas, Cushing syndrome, failure of medical management of Cushing disease, etc.), nonfunctioning cortical adenomas, and isolated adrenal metastasis. Mean tumor size was 2.7 cm. Complications occurred in 11.2% of patients, with a significant decrease in the complication rate during the second half of the study. There was no perioperative mortality. Longer operative times were encountered in male patients, obese patients, and in patients with a right-sided lesion. Conversion to an open procedure was necessary in 6.6% of cases. Of note, 48% of the patients had a body mass index greater than 30. We have thus found PRA to be a safe and, in our hands, the preferred approach for resection of benign tumors and small adrenal metastases, generally avoiding difficulties encountered in patients with obese habitus or extensive adhesions secondary to prior abdominal surgery.

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17 Carcinoma of the Thyroid Gland and Neoplasms of the Parathyroid Glands

Kristin L. Long and Elizabeth G. Grubbs

THYROID GLAND

Introduction

Thyroid carcinoma represents the most common endocrine malignancy; with a steadily increasing incidence since the 1990s, in 2016 it became the most rapidly diagnosed cancer (>5% per year in both men and women). In particular, papillary thyroid carcinoma (PTC) now represents the fifth most common cancer in females. A substantial portion (up to 40% in 2009) of these cancers are diagnosed very early, with tumors measuring under 1 cm in size, and are considered microcarcinomas. The increase in thyroid cancer incidence is thought to be due, in large part, to "overdiagnosis" of these smaller carcinomas from increased use of imaging and diagnostic techniques. However, increases in the incidence rate and thyroid cancer mortality rate for advanced thyroid cancer have been recently observed in SEER data evaluated from 1974 to 2013 and may not be discounted. The relatively low death rate compared to incidence is due, in part, to the indolent nature of most thyroid cancers. While a small percentage of cases are the aggressive anaplastic variety, more than 90% of thyroid cancers are well differentiated and follow an indolent, protracted course. Patients with differentiated thyroid cancer (DTC) usually have an excellent long-term prognosis, with 5-year survival rates approaching 100% for localized disease.

The evaluation, screening, and management of malignant thyroid disease are continually evolving and new guidelines have been recently published regarding extent of surgical resection, role of lymphadenectomy, and adjuvant medical therapies for thyroid carcinoma. Additional advances in the fields of molecular and genetic testing have offered new avenues for the evaluation of these patients.

Pathology

Thyroid carcinomas can be classified into two main categories. Well-differentiated thyroid carcinoma, which includes papillary (PTC) and follicular thyroid carcinomas (FTC), accounts for the vast majority of disease. Poorly differentiated carcinoma includes medullary thyroid carcinoma (MTC) and anaplastic thyroid carcinoma (ATC), which together make up only 5% to 6% of thyroid cancer cases. Rare primary tumors of the thyroid gland can include lymphoma, squamous cell carcinoma, and sarcoma and the thyroid may serve as a metastatic site for other malignancies (most commonly renal cell, lung, or breast).

PTC and FTC are broadly categorized as DTCs but can be further subclassified based on their histologic appearance or biologic behavior (Table 17.1). PTC accounts for over 80% of all thyroid malignancies and is the predominate histology seen in patients exposed to radiation. The mean age at presentation is 30 to 40 years and females are more often affected than males (2:1 ratio). Macroscopically, the tumors tend to be sharply circumscribed and white in color. Unlike normal thyroid or benign colloid lesions that bulge upon sectioning, PTC remains flat. Diagnosis is made by microscopic evaluation and can be made on the basis of fine needle aspiration (FNA) prior to surgical intervention. Lesions often have papillary projections although a mixed papillary/follicular and pure follicular variant can sometimes be seen. A definitive diagnosis is made on the basis of cellular and nuclear characteristics with cells adopting a cuboidal shape with nuclear “grooving” and cytoplasmic inclusions. These characteristic findings are described as the pathognomonic “Orphan Annie” nuclei. Psammoma bodies, present in 50% of specimens, help to secure the diagnosis of PTC and represent calcified deposits of sloughed cells that have been deposited in the stroma or lymphatics. PTC is characterized by multifocality in up to 80% of patients and is associated with an increased risk of lymph node metastasis. Cervical lymph node metastases are fairly common in patients with PTC at presentation with a frequency ranging from 30% to 80% in the literature and are often microscopic in size. Despite this high incidence, the 10-year survival rate is still 95%. Recently, the encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) has been shown to demonstrate extremely low risk of adverse outcomes and has been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) to guide treatment recommendations, predominantly in the postoperative

period.

TABLE 17.1 Pathologic Classification of Thyroid Malignancies

Subtype	Variants	Incidence
Well Differentiated		
Papillary (80%)	Conventional	65–85%
	Follicular	15–20%
	Tall cell	5–10%
	Solid	1–3%
	Diffuse sclerosing	1–2%
	Columnar	<1%
Follicular (10%)	Hürthle cell variant	
Hürthle Cell (5%)		
Poorly Differentiated	Insular	
Medullary (5%)		
Anaplastic (1–5%)		
Other	Lymphoma	
	Metastatic	

Incidence is representative for each variant of a particular subtype.

The second most common thyroid cancer is FTC which represents approximately 6% to 10% of all thyroid malignancies. These tumors are most often found in iodine-deficient areas and like PTC, have a female predominance with a 3:1 (female:male) ratio. FTC is often found in association with benign thyroid disorders, such as endemic goiter, and a relationship between TSH stimulation and follicular carcinoma has been suggested because of the greater incidence of FTC in iodine-deficient areas. The mean age at diagnosis is approximately 10 years later than those with PTC, presenting in the fifth to sixth decades of life. Patients usually present with a history of a solitary nodule, sometimes with a rapid increase in size. FTCs are usually unifocal, well-encapsulated lesions containing highly cellular follicles, and are easily confused with benign follicular adenomas on FNA. Pathologic diagnosis of this malignancy can only be made by permanent sectioning, demonstrating the presence of capsular or vascular invasion. FTC is divided into widely invasive (i.e., gross invasion) and minimally invasive with the later further risk-stratified by degree of microscopic vascular and capsular invasion. Metastasis to the

cervical lymph nodes is uncommon with FTC, being present in 5% to 10% of cases at initial presentation. Distant disease is more common at initial presentation and is seen in 10% to 33% of patients, most often presenting with hematologic spread to the lungs or bone. Ten-year survival rates for FTC are 70% to 95%, slightly worse than those for PTC, which is possibly due to later presentation and presence of distant metastases at the initial diagnosis. Hürthle (oncocytic) cell carcinoma, with its characteristic voluminous mitochondrial-rich follicular cells, is often thought to be a variant of FTC, though the subtype retains a distinct molecular signature.

TABLE 17.2 Hereditary Syndromes Associated with Increased Risk of Thyroid Cancer

- Familial adenomatous polyposis (PTC; inactivating mutations of *APC*)
- Cowden disease (PTC, FTC; *PTEN* mutation)
- Werner syndrome (PTC, FTC, ATC; *WRN* mutation)
- Carney complex (PTC, FTC; *PRKAR1a* mutation)
- Multiple endocrine neoplasia 2A and 2B (MTC; *RET* proto-oncogene mutations)

Various subtypes of thyroid cancer can be seen in hereditary syndromes (see Table 17.2). In particular, MTC, which represents 4% to 5% of all thyroid malignancies is frequently seen as a component of hereditary endocrine syndromes such as multiple endocrine neoplasia 2 (MEN2). The majority (75%) of MTC cases remain sporadic, however. MTC, particularly when associated with familial syndromes, often presents in the third to fourth decades of life and is frequently multifocal in these cases. Sporadic MTC tends to present slightly later and is most commonly unifocal in nature. Because MTC arises from the C cells, these tumors are localized to the upper poles of the thyroid gland where C cells reside. The presence of C-cell hyperplasia is thought to be a harbinger for the development of hereditary MTC. These lesions are nonencapsulated and ill-defined, consisting of a heterogeneous mix of spindle-shaped or round cells. The cells are separated by fibrous septa and amyloid, the latter of which aids in the diagnosis of MTC by immunohistochemical (IHC) staining as does staining for calcitonin and carcinoembryonic antigen (CEA). Although these tumors grow slowly, they have a propensity to metastasize early, usually before the primary tumor has reached 2 cm. Cervical and upper mediastinal lymph nodes are typically the first areas

involved with metastatic disease and 50% of patients will have regional metastases at the time of diagnosis. The survival for patients with MTC lies between that of differentiated and undifferentiated (anaplastic) thyroid cancers. When disease is confined to the thyroid gland, the 10-year survival rate is 90% versus patients with distant metastatic disease having a 10-year survival of only 20%.

ATC is the most aggressive and subsequently most lethal variety of thyroid malignancy. It is hypothesized that ATC may originate from a focus of well-differentiated thyroid carcinoma (DTC) that de-differentiates over time and becomes alarmingly aggressive. True ATC is quite rare, and comprises only 1% to 2% of all thyroid carcinomas diagnosed. The peak incidence is in the seventh decade of life, and survival is very poor (25% and 5% at 1 year and 5 years, respectively). Patients usually present with a rapidly growing mass and symptoms of dysphagia, dysphonia, or dyspnea secondary to compressive symptoms from the mass which is often fixed to underlying structures and often unresectable at the time of initial presentation. The tumor is nonencapsulated and often contains areas of necrosis which may result in a nondiagnostic FNA and require a core (preferably) or incisional biopsy to secure a diagnosis in addition to ruling out lymphoma. The cells are characteristically large and multinucleated with nuclear polymorphism and a high mitotic activity. At presentation, 25% of patients will have tracheal invasion, 90% will have regional metastases, and 50% will have distant spread, most commonly to the lung. Historically, surgery rarely played a role in this disease; however, as new treatment options are developed that may slow growth or show significant tumor response, surgical discussion (both curative and palliative) has become more common.

Primary thyroid lymphoma (PTL) is seen more frequently in women (2–8:1), particularly those with a history of Hashimoto thyroiditis. PTL comprises less than 5% of thyroid malignancies and <2% of extranodal lymphomas. This disease may present with a rapidly growing mass, dysphagia, or dysphonia, and can be confused with ATC. Diagnosis is based on morphologic features as well as immunophenotypic, cytogenic, and molecular profiles. Cellular yield for flow cytometry may be higher by FNA than by core biopsy, suggesting an adjunctive role of these diagnostic modalities. Patients with disease localized to the thyroid gland have favorable survival (75% to 85% 5-year survival), however if the disease is disseminated or present on both sides of the diaphragm, survival is

markedly worsened.

Diagnosis

Thyroid pathology is often diagnosed incidentally, during routine physical examination/palpation or by neck imaging performed for unrelated issues (computed tomography, neck ultrasound, positron emission tomography, or ultrasonography). Increasingly, thyroid nodules are found on routine health maintenance examinations which often include a cursory neck ultrasound evaluating vascular disease. High-resolution ultrasound can detect thyroid nodules in up to 68% of randomly selected individuals. Occasionally, patients may seek treatment for symptoms of a palpable neck mass, compressive symptomatology, or voice/swallowing changes. Significant dysphagia, dysphonia, dyspnea, or hemoptysis may result from local invasion and can signal aggressive pathology.

Particular attention to a prior history of radiation exposure, family history of thyroid or other endocrine malignancies, personal history of malignancy, or prior neck surgeries should be noted in the initial physical examination. Uniquely, the presence of pain on palpation, significant flushing or diarrhea may raise the possibility of a diagnosis of MTC. Examination for any palpable cervical adenopathy, particularly along the mid to lower jugular chains, serves as an adjunct to high-resolution ultrasound imaging. Radiographic evaluation of the thyroid gland and the central and lateral cervical compartments is an essential part of the workup of a thyroid nodule. Ultrasonography is the preferred modality, however, cross-sectional imaging may provide additional information, especially in cases of advanced malignancies. The degree of neck extension should be evaluated prior to any surgical planning, as should vocal cord function (including visualization in patients with a history of prior neck surgery or new voice changes).

Initial laboratory assessment of thyroid function should include measurement of thyroid-stimulating hormone (TSH).

Once a thyroid nodule is identified, the presence of malignancy should be excluded if appropriate, often as guided by ultrasonographic appearance of the lesion. The 2015 American Thyroid Association Guidelines recommend FNA biopsy based on size and sonographic patterns as illustrated in Figure 17.1; diagnostic FNA is recommended for nodules ≥1 cm in greatest dimension with high or intermediate suspicion sonographic patterns and nodules ≥1.5 cm in greatest dimension with low suspicion

sonographic pattern. Diagnostic FNA may be considered for nodules ≥2 cm in greatest dimension with very low suspicion pattern; observation without FNA is also a reasonable option in this group. Diagnostic FNA is not recommended for nodules that are purely cystic. Certain patterns and characteristics described in Figure 17.1 may increase the suspicion of identifying a thyroid malignancy, and may prompt FNA to be performed even on nodules smaller than the currently recommended size criteria.

FNA of thyroid lesions is a safe and cost-effective means to diagnose a thyroid malignancy; it provides direct diagnostic information on a lesion and has the greatest accuracy for lesions that are 1 to 4 cm. Lesions that are less than 1 cm are more difficult to sample, even with ultrasound, while lesions that are greater than 4 cm have a greater chance for sampling error because of their larger size. The accuracy of FNA to diagnose a thyroid malignancy can be as high as 90% with a false-negative rate of less than 5% when an experienced physician performs the procedure and the collected cells are evaluated by an experienced cytopathologist. FNA cytology results should be reported using the Bethesda System for Reporting Thyroid Cytopathology, a consensus recommendation created from a National Cancer Institute State of the Science Conference in 2007. As described in Table 17.3, the system describes six diagnostic categories and an estimation of cancer risk for each. Lesions sampled by FNA are classified as benign, follicular lesion of undetermined significance, neoplasm (follicular or Hürthle cell variety), suspicious for malignancy, malignant, or nondiagnostic. The cytologic diagnosis achieved by FNA plays a critical role in the subsequent treatment algorithm of patients with a thyroid nodule (Table 17.3). Because true rates of malignancy are institution-specific and depend on the experience of the physician performing the FNA as well as the pathologist interpreting it, the cytology must be carefully interpreted.

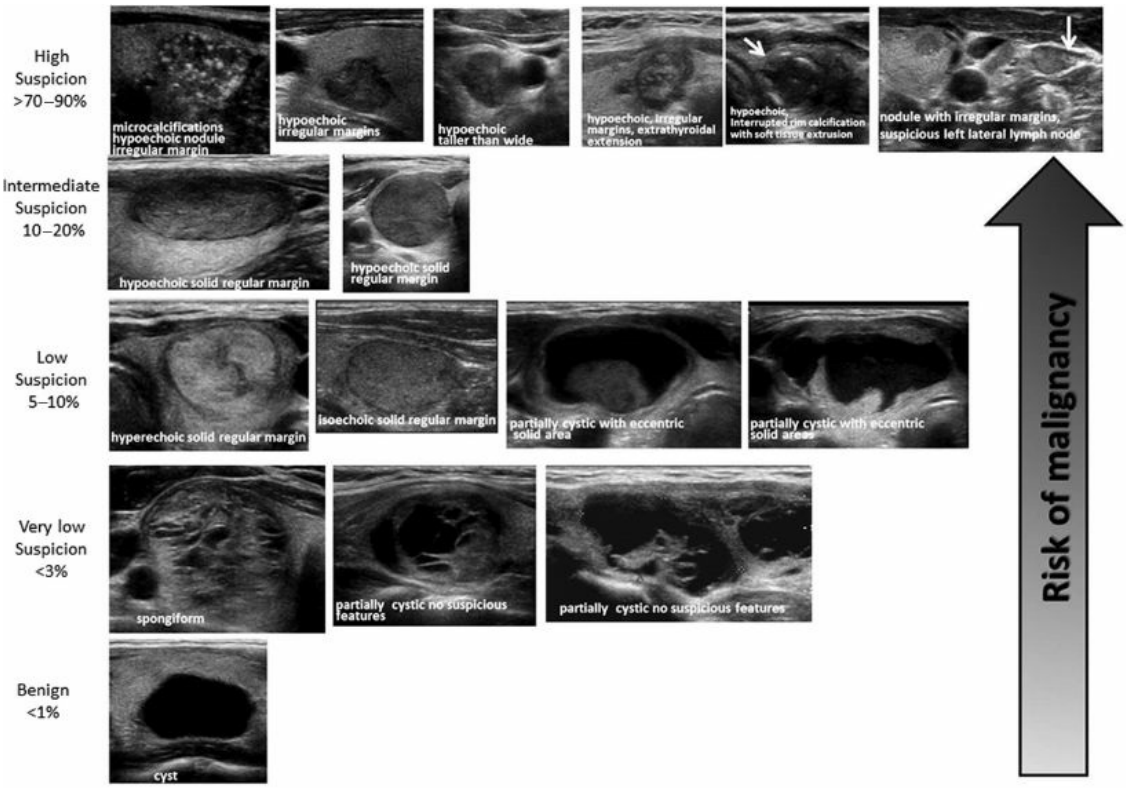


Figure 17.1 American Thyroid Association—Guidelines for Thyroid Biopsy. (Reprinted with permission from Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26(1):1–133. doi:10.1089/thy.2015.0020.)

TABLE **17.3** The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Usual Management

Diagnostic Category	Estimated Risk of Malignancy (%)	Usual Management
Nondiagnostic	1–4	Repeat FNA with ultrasound guidance
Benign	0–3	Clinical follow-up
Atypical cells of undetermined significance (ACUS), follicular lesion of undetermined significance (FLUS)	5–15	Clinical/imaging correlation, repeat FNA for most
Follicular neoplasm or suspicious for a follicular neoplasm • Specify if Hürthle cell type	15–30	Surgical lobectomy
• Suspicious for malignancy • Suspicious for papillary carcinoma • Suspicious for medullary carcinoma • Suspicious for lymphoma • Suspicious for metastatic tumor • Other	60–75	Total thyroidectomy or surgical lobectomy
Malignant	97–99	Total thyroidectomy

Adapted with permission from Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology. *Am J Clin Pathol* 2009;132(5):658–665.

The risk of malignancy for a specimen categorized as “benign” on FNA is <1% while those labeled “malignant” have up to a 100% risk of malignancy. Clinical decision making and knowledge of malignancy play the most important role for those lesions categorized as “follicular lesion of undetermined significance,” “neoplasm,” or “suspicious for malignancy.” Follicular lesions of undetermined significance have a 5% to 10% risk of malignancy and are a heterogeneous group of lesions that are not convincingly benign, yet lack characteristics to label them as a follicular neoplasm or suspicious for malignancy. Often this is secondary to inferior quality of a specimen either from hypocellularity, poor fixation techniques, or presence of blood that obscures the sampled cells. In these cases, a repeat FNA can be beneficial. FNA samples that are categorized as “follicular/Hürthle cell neoplasm” (also denoted as “suspicious for follicular/Hürthle cell neoplasm”) have a 15% to 45% risk of malignancy and usual management involves surgical resection so that a definitive pathologic diagnosis may be rendered. In some cases, molecular testing, which is now readily available, may help to guide decision making regarding indeterminate nodules. Finally, lesions that are read as “suspicious for malignancy” are malignant 60% to 75% of the time. When a lesion is suspicious for a papillary malignancy, these are most often

follicular variants of PTC.

Although PTC, MTC, and ATC can often be diagnosed by FNA (or a core biopsy in the case of ATC), the distinction between FTC and a follicular adenoma cannot be made solely on FNA because the presence of vascular or capsule invasion must be confirmed in order to diagnose FTC. This cannot be achieved with FNA alone and a tissue sample, usually in the form of a thyroid lobectomy, is needed in order to ascertain whether malignancy is present. Intraoperative frozen section evaluation of follicular neoplasms at the time of lobectomy is usually not definitive and we do not routinely recommend this practice. In cases where the FNA of a nodule is nondiagnostic, the patient should undergo a repeat FNA or surgery to obtain adequate tissue for diagnosis. In 15% to 25% of cases, the FNA will not yield enough material for diagnosis and a repeat FNA is necessary. Ultrasound, with its increased utilization and technologic advancements, has increased the yield of FNA and reduced the need for repeat aspirations.

Additionally, for larger tumors (>4 cm), suspected local invasion, or in patients with palpable nodal disease, use of cross-sectional imaging (computed tomography) has become increasingly common for preoperative planning, and is now recommended in the newest ATA guidelines.

Genetics and Molecular Markers

Over the past decade, significant progress has been made in the identification of genes linked to the pathogenesis of thyroid cancer. Studies of the patterns of genetic alterations present in thyroid tumors suggest that there are differences in the pathogenesis of the different thyroid tumor types, which most likely accounts for the range of biologic behavior observed among thyroid cancers. The genomic landscape of PTC was recently described as part of The Cancer Genome Atlas (TCGA) project in which a low frequency of somatic mutations was found compared to other carcinomas and there was a dominant role and mutual exclusivity of driving somatic gene mutations in the MAPK and PI3K pathways. In approximately 50% of cases (60% in TCGA), a constitutive activation of the BRAF kinase, a member of the *Ras/MAPK* pathway, is present and usually results from a V600E amino acid substitution. BRAF is normally dependent on *Ras* activation in order to propagate extracellular signal transduction. The TCGA work indicated that *BRAF*^{V600E} PTC

represents a diverse group of tumors and should not be considered a homogeneous group; further studies are necessary to capture their genetic diversity. In certain scenarios, activation of the *Ras* oncogene, upstream of BRAF, has also been implicated as an initiating event in PTC, as well as follicular thyroid cancer. Somatic mutations in the *Ras* oncogene (H-,K-,N-Ras) have been found in both benign and malignant thyroid tumors (12% of PTC in TCGA), and thus seem to be an early event in thyroid tumorigenesis. Some reports suggest that *Ras* mutations are more prevalent in follicular thyroid cancers (FTCs), follicular variant of PTC, and follicular adenomas. Mutations in *Ras* may result in allelic loss or in chromosomal rearrangements leading to increased rates of follicular thyroid cancer formation. Signaling differences exist in *Ras*- and *BRAF*^{V600E} driven PTCs; BRAF-like PTCs signal primarily through MAPK while *Ras*-like PTCs signal through both MAPK and PI3K; this may have wide spread implications for targeted therapies. Chromosomal rearrangements have also been observed in RET/PTC fusion oncogene formation; radiation-induced PTCs harbor this alteration. Additional rare oncogenic fusions described in PTC include *BRAF*, *PAX8/PPARG*, *ETV6/NTRK3*, and *RBPMS/NTRK3*. Other less common driver mutations include *EIF1AX*, *PPM1D*, and *CHEK2*.

The *RET* proto-oncogene is a tyrosine kinase receptor that is mainly expressed in tumors of neural crest origin, explaining the high incidence of mutations in medullary thyroid cancers (MTCs) which originate from the parafollicular cells (C cells). The *RET* gene is located on chromosome 10 and germline mutations result in missense activating mutations which are responsible for 95% of inherited MTC, including those associated with multiple endocrine neoplasia 2A and 2B (MEN2A/B). In 80% of cases of MTC, the disease is sporadic, without an inherited etiology but a somatic mutation in *RET* is identified in 40% of these sporadic cases. In these sporadic cases, mutations are most often found in codon 918 which results in constitutive activation of the *RET* tyrosine kinase receptor. Nearly all patients with autosomal dominant MEN 2A or MEN 2B will develop MTC and screening for germline *RET* mutations has been invaluable in the early identification of patients who have a genetic basis for their disease. Even in patients with sporadic MTC, 6% to 10% of these patients will have an *RET* proto-oncogene germline mutation, thus revealing a new kindred of patients with previously undiagnosed MTC. The discovery of the *RET* proto-oncogene has had significant clinical impact, affecting the screening

and prophylactic treatment of patients who are members of the MEN and familial MTC kindreds. A somatic *Ras* mutation occurs in approximately 15% of patients with sporadic MTC.

Anaplastic thyroid cancer (ATC) develops from the dedifferentiation of thyroid tumors although no specific inciting event has been elucidated to cause the transformation. Mutations in the *p53* tumor-suppressor gene are frequently found in ATC and are absent in well-differentiated thyroid neoplasms. This observation suggests that *p53* mutations play a role later in thyroid tumor pathogenesis—specifically, in the dedifferentiating transition to the anaplastic phenotype. A myriad of mutations in other pathways including the PI3K/Akt and Ras/MAPK pathways have also been implicated in the formation of ATC.

Despite the tremendous work that has been performed to solidify the role of the *RET* tyrosine kinase receptor in medullary thyroid tumor initiation, as well as the role of *Ras* and BRAF in PTCs and FTCs, much work is still needed to detail the signaling pathways that lead to tumor progression and aggressiveness and that will ultimately translate into improved clinical management for patients who suffer from this disease.

Treatment

Once a thyroid malignancy is definitively diagnosed (and in some cases, when more tissue is necessary to appropriately classify a thyroid nodule), surgical resection should be considered. The goal remains complete clearance of disease with minimal morbidity or loss of function. Appropriate surgical treatment will allow careful postoperative screening, adjuvant therapies if necessary, and minimizes the chance of disease recurrence.

In light of the low mortality rate associated with PTC, recurrence of disease has become the primary outcome of interest when deciding upon the optimal surgical treatment plan for the majority of patients. For patients with PTC measuring greater than 1 cm, surgery has historically consisted of a total thyroidectomy which certainly remains the appropriate operation for high-risk well-differentiated thyroid cancers (WDTC). The 2015 ATA guidelines were revised to state that in 1 to 4 cm WDTC without extra-thyroidal extension or lymph node metastases, either a lobectomy or total thyroidectomy is acceptable treatment. From the studies available, the majority retrospective, total thyroidectomy does have a small, but statistically significant improvement in disease-free survival.

From an oncologic standpoint, either lobectomy or total thyroidectomy has similar disease-specific survivals. That being said, the low incidence of recurrent laryngeal nerve (RLN) injury or permanent hypoparathyroidism (2%) in surgeries performed by experienced surgeons makes total thyroidectomy a reasonable choice for low risk, 1 to 4 cm disease when performed by an experienced surgical group. Reasons to consider performance of a total thyroidectomy in low-risk WDTC include lesions observed within the contralateral lobe on imaging; foci of PTC are found bilaterally in up to 85% of thyroid specimens and 5% to 10% of recurrent disease occurs in the contralateral lobe when a thyroid lobectomy is performed. From a postoperative standpoint, the thyroid tissue that remains, if a more conservative resection is undertaken, makes radioactive iodine (RAI) ablation of the remaining gland prohibitive. In addition, serum measurement of thyroglobulin as a marker of persistent or recurrent disease after thyroid lobectomy is more difficult to interpret given the remaining thyroid tissue. A total thyroidectomy avoids these pitfalls and minimizes reoperative surgery which is associated with increased complication rates. Patients in whom postoperative RAI is planned should undergo total thyroidectomy (i.e., familial PTC, bilateral disease, radiation exposure). These benefits must be weighed against the absolute requirement for lifelong thyroid hormone replacement necessary with total thyroidectomy and the knowledge that while complications occur less frequently when operations are performed by experienced surgeons, the extent of surgery can increase the risk of complications, irrespective of surgeon volume.

On the basis of the data and advantages described above, our usual management is to perform a thyroid lobectomy for patients with PTC, FTC, and Hürthle cell carcinoma less than 1 cm (refer to the Multiple Endocrine Neoplasia section of Chapter 15 for recommended surgical management of MTC). In patients with well-differentiated cancers measuring 1 to 4 cm, factors in addition to tumor size, such as contralateral thyroid nodules, other coexistent thyroid pathology, radiographic concern for gross extrathyroidal extension, and presence of locoregional and/or distant metastasis, are relevant to decision making as to the extent of thyroidectomy; each patient presents with their unique set of risk factors. Patient preference must also be factored into the treatment discussion. Unfortunately, the diagnosis of FTC or Hürthle cell carcinoma cannot be made utilizing FNA, for reasons noted above, and cannot be readily

ascertained on the basis of frozen section evaluation intraoperatively. Usually the diagnosis of FTC or Hürthle cell carcinoma is made postoperatively, in a patient who has already undergone a thyroid lobectomy. In these circumstances, a completion thyroidectomy is often performed in high-risk patients when RAI is planned, as all gross thyroid tissue must be removed for RAI to be effective.

Anaplastic carcinoma presents a unique challenge because it is rarely diagnosed in a timely fashion such that surgical management is usually only offered as a palliative option. In the rare instance where anaplastic carcinoma has been diagnosed either incidentally or early in its course, total thyroidectomy with central and ipsilateral modified radical lymphadenectomy offers the best opportunity for survival in the rare event that the tumor is intrathyroidal. Given the aggressive nature and limited survival for patients with anaplastic carcinoma, extended surgical intervention involving resection of adjacent structures, such as the larynx, pharynx, or esophagus, is often avoided due to the associated excessive morbidity. Resection of disease that extends beyond the thyroid gland may be appropriate in highly selected individuals as part of a multimodality treatment regimen along with radiation and chemotherapy.

In most cases of appropriately treated DTC, patients have a good prognosis with 10-year survival rates greater than 75% likely due to the indolent course of the disease. Controversy exists surrounding the performance and extent of prophylactic lymph node dissection in order to prevent local recurrence, provide more accurate staging, and increase survival. The distinction between a therapeutic versus prophylactic (or elective) central compartment dissection is that a therapeutic dissection implies that nodal disease has already occurred and been detected either clinically or by preoperative imaging (N1 disease). An elective or prophylactic central compartment dissection implies that there is no clinical or radiographic evidence for nodal metastases. This distinction is important because the impact of clinically detectable lymph node involvement on survival and local recurrence may differ from that observed with microscopic disease. Additionally, a central neck dissection may be ipsilateral (same side as the dominant tumor) or bilateral (ipsilateral and contralateral) and it is important to document this distinction in the operative note.

For PTC, performance of prophylactic central lymphadenectomy is surgeon dependent. We perform a prophylactic ipsilateral central neck

dissection on an individual case basis, often for primary tumors >4 cm or when extrathyroidal extension is diagnosed either preoperatively or at the time of surgery. Therapeutic bilateral central lymph node dissection (level VI) is appropriate if there is preoperative biopsy-proven central or lateral compartment disease or central compartment nodal disease that is found intraoperatively. For patients with biopsy-proven cervical lymph node metastases, a therapeutic lateral lymph node dissection is performed (levels IIa to IV with the addition of levels IIb, V, and VII based on the preoperative imaging or intraoperative findings).

Given the low incidence of lymph node metastases with FTC, we do not routinely perform lymphadenectomy unless there is palpable lymphadenopathy at the time of surgery or preoperative ultrasonography demonstrates suspicious nodes.

MTC is treated with a total thyroidectomy and bilateral prophylactic central neck dissections. Should ultrasound demonstrate any evidence of nodal involvement in the lateral neck, therapeutic lateral neck dissection is performed as well.

Surgical Technique

The neck is an anatomically complex site and removal of the thyroid gland requires precision and vigilance in identifying and preserving critical structures in this region. After the induction of general endotracheal anesthesia, the patient's arms are tucked and placed in the semi-Fowler position with the neck hyperextended using a shoulder roll and appropriate support behind the head. Again, the patient's ability to extend their neck should be ascertained preoperatively so as to not induce trauma during operative positioning. The field is then prepped and draped in the usual sterile fashion to include the chin, neck, and chest.

A transverse incision, preferably utilizing a skin crease for cosmesis, is made approximately one to two fingerbreadths above the suprasternal notch. Electrocautery is used to divide the platysma and flaps are created in the subplatysmal plane both superiorly and inferiorly to the level of the thyroid notch and suprasternal notch, respectively. The strap muscles are then separated vertically along the median raphe. Strap muscles adherent to the gland or tumor should be resected en bloc with the specimen. In cases of reoperation, the thyroid compartment may be approached laterally along the anterior border of the sternocleidomastoid muscle.

Once proper exposure has been obtained, the sternothyroid muscle is

freed from the underlying thyroid (unless precluded by tumor involvement in which case the muscle is resected en bloc with the thyroid) and the lobe of interest is retracted medially in order to identify and ligate the middle thyroid vein. This allows further medial mobilization of the lobe in order to enter the tracheoesophageal groove and identify and preserve the RLN as it runs caudally to cephalad. In approximately 1% of patients, a non-recurrent RLN is present on the right side and can be identified as it originates from the vagus nerve proximally.

A Kittner dissector is useful to perform gentle blunt dissection medial to the carotid artery to delineate the paratracheal groove and is carried inferiorly from the thoracic inlet to superiorly at the superior pole vessels. At the superior pole, the external branch of the superior laryngeal nerve can be injured as it enters the cricothyroid muscle, resulting in difficulty with high-pitched tones. This nerve has a variable course and is intimately associated with the superior thyroid vessels in approximately 58% of the cases, either by traveling between branches of the superior thyroid artery, running in close proximately (<1 cm) superior to the vessels, or coursing posterior to the vessels and superior pole of the thyroid gland. The superior pole vessels must therefore be meticulously dissected close to the thyroid gland and divided individually, rather than placing a clamp across all superior pole structures blindly. The RLN is best found low in the paratracheal groove as it travels caudal to cephalad, its identification often enhanced by initial release of the superior pole. In this dissection, the inferior thyroidal artery will be encountered; the RLN often runs posterior to this artery but may run between its branches or anterior to the artery as well. In 20% of cases, the nerve branches in this region and these branches should be preserved. The inferior thyroid artery branches, like the superior branches, must be individually ligated at the level of the thyroid gland in order to prevent injury to the RLN. Careful dissection of the inferior thyroid artery is not only meant to prevent RLN injury but also to maintain the blood supply to the parathyroid glands. The most common reason for postoperative hypoparathyroidism is compromise of this vascular supply during surgery. The superior parathyroid gland is usually located within the thyroid fascia and located within 1 cm of the intersection of the RLN and inferior thyroid artery in 80% of cases. The inferior parathyroid gland has a more variable location but is typically located posterior and medial to the RLN near the inferior pole of the thyroid gland in the thyrothymic tract. The parathyroid glands are carefully dissected free from the thyroid

paying special attention to preserve the lateral vascular pedicle. On occasion, a small rim of thyroid tissue may need to be preserved in order to protect the vascular supply to the parathyroid glands. Should the vascular supply be compromised, the parathyroid gland should be carefully minced and autotransplanted into the ipsilateral sternocleidomastoid muscle after its identity has been confirmed on immediate pathologic evaluation. Resection of the contralateral thyroid lobe, when indicated, proceeds in the same manner as described above.

A central compartment (level VI) lymph node dissection is performed to remove lymphatic tissue bordered superiorly by the hyoid bone, inferiorly by the level of the innominate artery, and laterally by the carotid arteries with special attention to remove all lymphatic and areolar tissue posterior to the RLN (Fig. 17.2). The goal is to clear all prelaryngeal, pretracheal, and paratracheal lymphatic tissue on the side of the tumor. If macroscopic lymphatic disease is observed in the contralateral neck, a contralateral central compartment dissection should also be performed; the role of such a dissection in the absence of gross disease is controversial and left to the individual surgeon's discretion. Isolated removal of only grossly involved lymph nodes, referred to as "berry picking," violates the nodal compartment entered without adequately addressing the full extent of its disease and may be associated with higher recurrence rates and morbidity from revision surgery. This technique should be discouraged in favor of the more oncologically sound anatomically based technique described above. Level VII lymph nodes are located in the superior mediastinum inferior to the plane of the innominate artery. This basin is not usually included in a central compartment neck dissection, however if gross disease is identified, transcervical access is feasible; partial or complete sternotomy may be utilized but is rarely necessary.

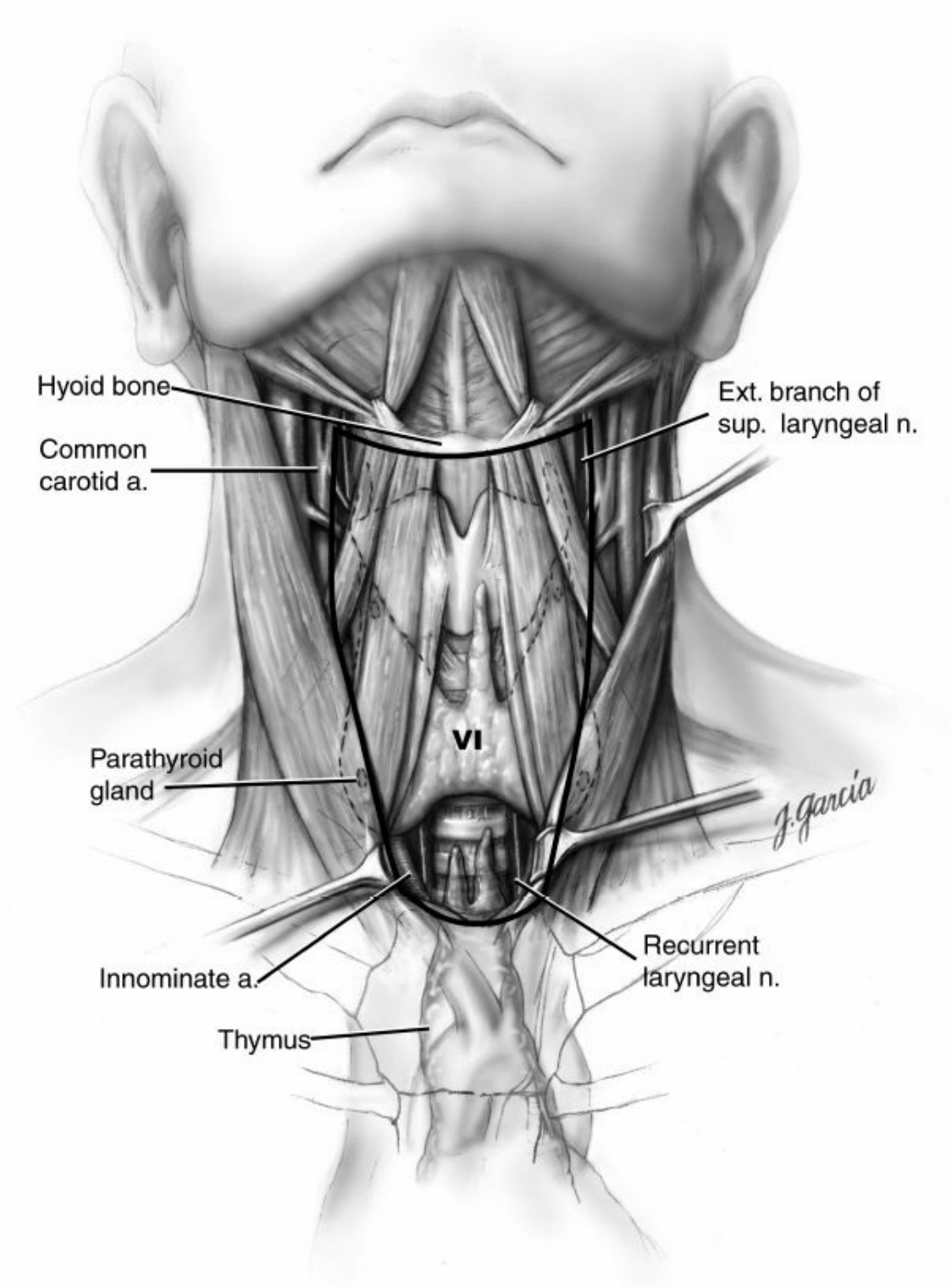


Figure 17.2 Anatomic boundaries of the central neck compartment. (Reprinted with permission from Carty SE, Cooper DS, Doherty GM, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid* 2009;19:1153–1158.)

When the removal of lateral lymph nodes is indicated for metastatic

disease, a modified radical neck dissection is performed, removing all lymphatic tissue in levels II through V while sparing the sternocleidomastoid muscle, spinal accessory nerve, vagus nerve, phrenic nerve, and internal jugular vein when possible (Fig. 17.3). Routine inclusion of level IIb and Va in a lateral compartment neck dissection is usually not performed; inclusion of these groups depends on burden of disease in adjacent compartments. The borders of a lateral compartment neck dissection are defined posteriorly by the anterior border of the trapezius muscle (posterior aspect of level V), inferiorly by the clavicle (inferior aspect of levels IV and V), medially by the lateral limit of the sternohyoid muscle (medial aspect of levels III and IV), and superiorly by the lower border of the body of the mandible and skull base (superior aspect of level II). Although extrathyroidal extension is rare for most thyroid carcinomas, the surgeon must be prepared to resect any invaded structures including laryngeal or spinal accessory nerves, muscle, tracheal rings, or laryngeal cartilage.

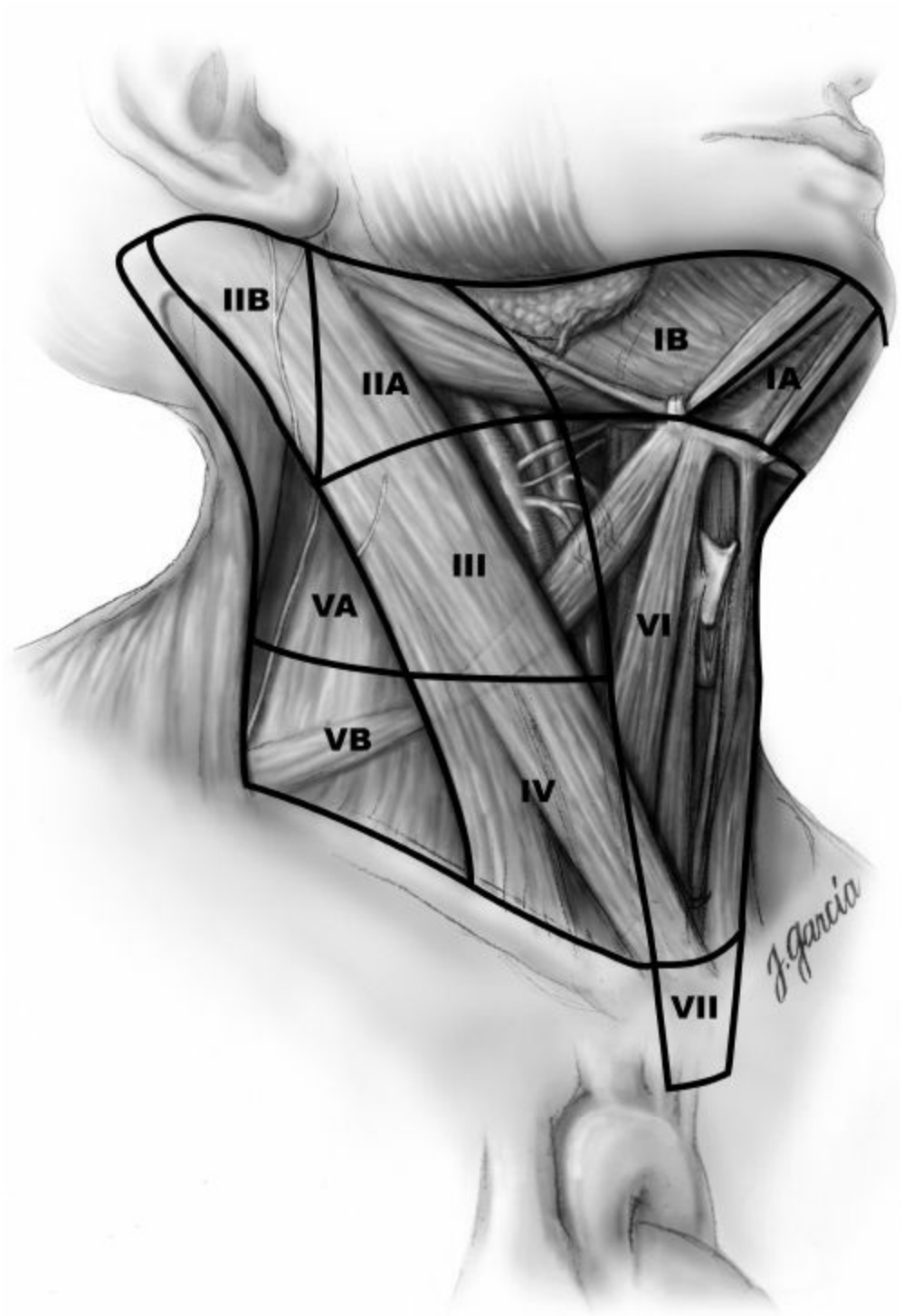


Figure 17.3 Anatomic compartments of the lateral neck. (Reprinted with permission from Carty SE, Cooper DS, Doherty GM, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid* 2009;19:1153–1158.)

Extent of Surgery

For PTC, therapeutic bilateral central neck lymph node dissection (level

VI) is appropriate if there is biopsy-proven central or lateral compartment disease prior to operation or central compartment nodal disease is found at the time of surgery. Prophylactic unilateral/ipsilateral central lymph node dissection can be considered appropriate for primary tumors greater than 4 cm or when extrathyroidal extension is appreciated at the time of surgery. Any prophylactic lymph node dissection should be performed weighing the potential benefits for the individual patient with the associated risks of aparathyroidism and RLN injury. Therapeutic lateral lymph node dissection is appropriate for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. This dissection routinely includes levels IIA, III, and IV with the addition of levels IIB and V as warranted by preoperative imaging or intraoperative findings.

For FTC and Hürthle cell cancer, no central or lateral neck dissection is indicated unless there is biopsy-proven disease prior to surgery or palpable disease is found at the time of surgery. Regarding ATC, given the aggressive nature of this disease, surgical intervention associated with excessive morbidity should be avoided; resections of the larynx, pharynx, and esophagus are discouraged. Surgical resection offers the best opportunity for survival if the tumor is intrathyroidal (rare). Resection of disease that extends beyond the thyroid may be appropriate in highly selected patients as part of multimodal therapy along with radiation and chemotherapy.

Staging

Thyroid carcinoma staging is most commonly performed using the American Joint Committee on Cancer (AJCC) staging system. A number of other validated staging systems have been used to predict cause-specific survival from thyroid cancer including AGES (Age, Grade, Extent, Size), AMES (Age, Metastasis, Extent, Size), MACIS (Metastasis, Age, Completeness of Resection, Invasion, and Size), and EORTC (European Organization for Research and Treatment of Cancer). Research has demonstrated the superiority of the AJCC TNM staging system in predicting cancer-related mortality. Unfortunately, no staging system, including the AJCC system, has a high predictive value in forecasting recurrent disease, especially in individuals who develop thyroid cancer at a young age.

The 8th edition (2016) of the AJCC staging system modified definitions of primary tumor and regional lymph node metastases (Table 17.4). Age at

diagnosis is perhaps one of the most important predictive factors for patients with DTC as evident from its inclusion in the AJCC as well as each of the other staging systems noted above. Male gender has also been shown to be an independent predictor of survival, as thyroid cancer is more aggressive in men, although this variable is not specifically included in any staging system. In general, the prognosis of patients with well-differentiated thyroid carcinoma is based on their age, gender, extent of disease, and the size of their primary tumor. The issue of lymph node metastases and prognosis is still debated since lymph node involvement predicts local recurrence but does not contribute significantly to patient survival. Lymph node involvement affects staging classification only in those patients older than 55 years of age.

TABLE 17.4 AJCC Staging System for Thyroid Cancer

Definition of Primary Tumor (T)

Papillary, Follicular, Poorly Differentiated, Hürthle Cell and Anaplastic Thyroid Carcinoma

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≥2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

Definition of Regional Lymph Node (N)

NX	Regional lymph nodes
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis

N1	Metastasis to regional nodes
N1a	Metastasis to level VI OR VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (level I, II, III, IV, or V) or retropharyngeal lymph nodes

Definition of Distant Metastasis (M)

M0	No distant metastasis
M1	Distant Metastasis

AJCC PROGNOSTIC STAGE GROUPS

Differentiated

When Age at Diagnosis is…	And T is…	And N is…	And M is…	Then the Stage Group is…
<55 years	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
≥55 years	T1	N0/NX	M0	I
≥55 years	T1	N1	M0	II
≥55 years	T2	N0/NX	M0	I
≥55 years	T2	N1	M0	II
≥ 55 years	T3a/T3b	Any N	M0	II
≥55 years	T4a	Any N	M0	III
≥55 years	T4b	Any N	M0	IVA
≥55 years	Any T	Any N	M1	IVB

Anaplastic

When T is…	And N is…	And M is…	Then the stage group is…
T1–T3a	N0/NX	M0	IVA
T1–T3a	N1	M0	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

Adapted from the *AJCC Cancer Staging Manual*, 8th edition.

The AJCC staging for thyroid cancer stratifies patients into four stages based on the TNM classification, except for ATCs, which are always considered stage IV. Staging is based on tumor histology and patient age (for differentiated cancer), demonstrating the importance of these parameters in survival and prognosis. The 8th edition of the AJCC staging system for thyroid cancer has been updated from prior editions by increasing the age at diagnosis cut-off point for DTC from 45 to 55 years.

Minor extrathyroidal extension was removed from the definition of T3 disease. T3a is now a new category and refers to tumors greater than 4 cm in greatest dimension but still limited to the thyroid gland. T3b is also a new category defined as a tumor of any size with gross extrathyroidal extension invading only the strap muscles. Importantly, the definition of central neck was expanded to include both level VI and level VII lymph nodes. Survival rates for the various thyroid cancers are presented in Table 17.5. Although similar for stage I disease, survival for FTC is slightly worse than PTC and is likely due to the propensity for hematogenous spread and later age and stage at presentation. ATC has one of the worst survival rates of all malignancies with a 1-year survival of 17% and a 5-year survival of approximately 6%, demonstrating the aggressiveness of this disease. In general, the prognosis for patients diagnosed with thyroid cancer is good with survival rates >85% to 90% for most stages, likely as a result of the indolent nature of the disease.

TABLE 17.5 Stage-Specific Relative Survival for Thyroid Cancer

	I	II	III	IV
Papillary				
1-Year	99.9	100	97.7	77.6
5-Year	99.8	100	93.3	50.7
Follicular				
1-Year	99.7	99.6	91.1	78.5
5-Year	99	99.7	71.1	50.4
Medullary				
1-Year	100	100	96	64.3
5-Year	100	97.9	81	27.7
Anaplastic				
1-Year	n/a	n/a	n/a	18
5-Year	n/a	n/a	n/a	6.9

All anaplastic thyroid cancers are considered stage IV.
Adapted from the *AJCC Staging Manual*, 7th edition.

Adjuvant Therapy

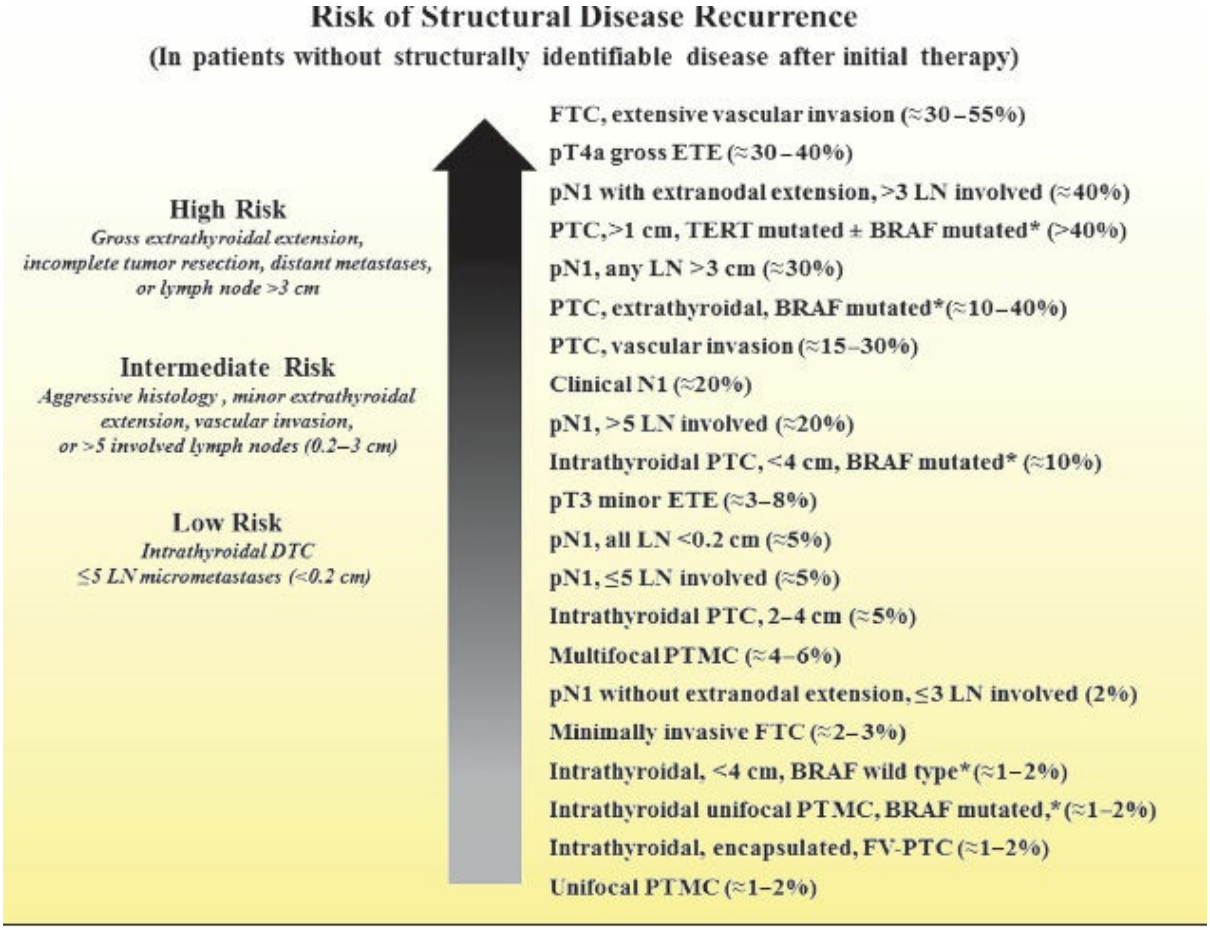
The goals of adjuvant treatment include prolonging survival and reducing the future recurrence of thyroid cancer. Retrospective studies of patient

cohorts followed postoperatively for several decades suggest that multimodality adjuvant therapy can decrease local recurrence and may improve survival. The ATA created and has recently revised an initial risk stratification system for DTC utilizing histology type, pathology characteristics, and mutational status (Table 17.6) to assist in decision making for the initiation of adjuvant therapy. The mainstay of adjuvant treatment for well-differentiated thyroid carcinoma is radioactive ^{131}I treatment and TSH suppression. The use of therapeutic radioactive ablation of remnant thyroid tissue after thyroidectomy is well established, but criteria for the use of this treatment vary among institutions.

The use of ^{131}I treatment after thyroidectomy improves clinical outcomes including recurrence and survival in selected patients with DTC. This advantage has been observed in patients with advanced disease (stages III and IV), while patients with small primary tumors confined to the thyroid usually do not benefit from RAI therapy. ^{131}I treatment is performed either through thyroid hormone withdrawal or using recombinant human TSH (rhTHS). Most DTC patients at MD Anderson Cancer Center (MDACC) undergo thyroid hormone withdrawal for 3 to 6 weeks along with 1 to 2 weeks of low iodine diet before ^{131}I therapy. Alternatively, rhTSH-assisted therapy is used, preferentially in patients who are at significant risk for side effects from hypothyroidism (elderly patients, cardiac patients, patients with spine or brain metastases) or patients with central hypothyroidism who cannot produce enough TSH to allow therapy. While 2 to 3 weeks of thyroid hormone withdrawal is usually sufficient to achieve the desired TSH level to proceed with ^{131}I treatment (TSH > 25 to 30 μIU/mL), patients undergoing prolonged thyroid hormone withdrawal (4 to 6 weeks) can take short-acting T3 (liothyronine) in the initial 2 weeks of withdrawal to ameliorate hypothyroid symptoms. While this practice is fairly common, the value of such an approach is unclear as most patients are asymptomatic in the initial few weeks of thyroid hormone withdrawal. Either ^{123}I or ^{131}I can be used to perform the initial diagnostic whole-body scan. At MDACC, ^{123}I is more commonly used due to factors related to imaging techniques and reducing the chance of theoretical tumor stunning effect. The initial diagnostic scan aids in disease staging and may assist with the decision to proceed with, as well as the dosing of ^{131}I therapy. ^{131}I therapy serves many goals including thyroid remnant ablation which simplifies future disease follow-up, as well as diagnosis and treatment of locoregional and

distant metastatic disease. Most ATA low-risk patients (intrathyroidal DTC without evidence of lymphovascular invasion, extrathyroidal extension or metastases; Table 17.6) do not receive ^{131}I; retrospective studies have shown no significant effect of RAI adjuvant therapy on overall or disease-free survival in this population. RAI ablation in DTC is primarily used for intermediate-risk (microscopic extrathyroidal extension, cervical lymph node metastasis, vascular invasion, or aggressive tumor histology) or high-risk (gross extrathyroidal extension, incomplete tumor resection, distant metastasis, or inappropriate postoperative serum thyroglobulin (Tg) levels) patients. Considering the risk:benefit ratio and the possibility of complications associated with ^{131}I therapy (including the small risk of secondary malignancies), lower doses are currently recommended compared to practices a decade ago. If RAI thyroid remnant ablation is utilized for ATA low-risk patients, a dose of 30 mCi is usually recommended. In higher-risk patients, where RAI is intended to treat microscopic residual disease, doses up to 150 mCi may be used.

TABLE 17.6 Risk Stratification System for Differentiated Thyroid Cancer



*Testing not routinely recommended.
Reprinted with permission from Haugen BR, Alexander EK, Bible KC, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26(1):1–133. doi:10.1089/thy.2015.0020.

After surgery and subsequent ^{131}I ablation therapy, patients receive hormonal replacement treatment (levothyroxine sodium) at a dose of 2 μg/kg/day. The dose may vary among patients and is adjusted to reach an appropriate level of TSH suppression for a patient as determined on the basis of the individual patient's risk status (Table 17.6). Patients with high-risk DTC are usually recommended for initial TSH suppression of below 0.1 mU/L and intermediate-risk patients are recommended for initial TSH suppression of 0.1 to 0.5 mU/L. Low-risk patients with undetectable serum Tg levels may be maintained at the lower end of the reference range (0.5 to 2 mU/L) while those with detectable Tg may be maintained at slightly below the lower limit of normal (0.1 to 0.5 mU/L). TSH suppression and RAI are of no use in the management of MTCs and ATCs because these tumors do not show consistent uptake of RAI and generally do not contain TSH receptors, making them insensitive to TSH suppression. The extent

and duration of TSH suppression is influenced by disease stage, status of recurrence, as well as other comorbidities that may exist in DTC patients (cardiac arrhythmias, coronary artery disease, osteoporosis, or psychological disorders). TSH suppression should be continually reevaluated based on the patient's disease status and altered when structural or biologically incomplete responses are noted.

The role of external-beam radiation therapy (EBRT) as part of the initial adjuvant treatment regimen for DTC is also controversial. Several retrospective series have reported that local control can be improved with EBRT, specifically in patients with gross residual disease following surgical resection or in patients considered to be at high risk of relapse; however, the potential side effects must be considered. Currently, EBRT is used rarely, most commonly to palliate metastatic or locally advanced disease, such as bone metastases or thyroid bed recurrences not amenable to further surgical resection, or in an attempt to avoid a more extensive surgery such as laryngectomy.

Overall, traditional cytotoxic chemotherapy has not been very effective in the treatment of thyroid carcinomas. Chemotherapy has limited use in the treatment of DTCs, Hürthle cell carcinomas, and MTCs. However, chemotherapy, in combination with EBRT and surgery, is more commonly used to treat ATC, for which there is a lack of effective therapies. Intravenous bisphosphonates can be given in patients with bony metastases. Arterial embolization has been used anecdotally to reduce pain in selected cases of metastatic FTC where the lesions are highly vascular.

In the past decade, major advancements in treating metastatic DTC and MTC have occurred. Many phase 2 studies have shown the benefit of targeted therapy to slow disease progression in as many as 60% to 70% of patients based on objective radiologic criteria. These agents resulted in few complete responses, while the majority of patients had either partial response or disease stability after documented progression and failure of ^{131}I treatments.

Multitarget tyrosine kinase inhibitors (TKIs) are now approved for the treatment of thyroid carcinoma. These agents primarily inhibit vascular endothelial growth factor receptor in addition to their effect on other tyrosine kinases. Pazopanib, sorafenib, and sunitinib are currently approved by the Food and Drug Administration (FDA) to treat various malignancies. In 2013, sorafenib (Nexavar) was approved for treatment of iodine-refractory DTC followed by lenvatinib (Lenvima) in 2015. These

kinase inhibitors are associated with adverse effects including hypertension, hand-foot skin reaction, diarrhea, rash, fatigue, weight loss, and stomatitis. Vandetanib (Caprelsa) and cabozantinib (Cometriq) have been approved for treatment of MTC. Additional research into further targeted therapies continues with the hopes of approval of other agents. Additionally, immunotherapy may provide an adjuvant approach, with trials currently being planned.

Surveillance

Most recurrences of DTC occur within the first 5 years after initial treatment, but recurrences can also occur several decades later. Patients with PTC often recur locoregionally in the neck, whereas patients with FTC more commonly recur at distant sites. MTC can recur locoregionally or distantly. The most common site of distant metastases for thyroid cancers are the lungs, bone, soft tissues, brain, liver, and adrenal glands. Lung metastases are more common in young patients, whereas bone metastases occur more often in older patients.

A coordinated plan of follow-up for thyroid carcinomas must consider the varied presentations possible for recurrent disease. Most patients are seen every 6 months for 1 to 3 years postoperatively and yearly thereafter. Follow-up visits for well-differentiated thyroid carcinoma patients typically include clinical examination and blood tests measuring the serum Tg, TSH, and free T4 levels as well as cervical ultrasonography. A thorough physical examination and ultrasonography should be performed in order to detect locoregional recurrences in the surgical bed or neighboring lymph node basins. Tg values normally drop after thyroidectomy and ablation and serve as a sensitive indicator of recurrent or persistent disease. However, it is important to keep in mind that Tg production is TSH dependent; therefore, TSH levels can affect the sensitivity of Tg measurements in detecting disease. As a result, stimulated serum Tg is often measured 1 year after initial treatment and is used to assess disease recurrence and plan future follow-up. In addition, 25% of patients with DTC have antithyroglobulin antibodies, which falsely lower measured Tg levels. Tg levels must always be interpreted in the setting of antithyroglobulin antibody status.

The surveillance for patients with MTC differs from FTC and PTC since it is not derived from follicular epithelium. Therefore, thyroid scanning and Tg measurement play no role in the detection of recurrent disease in

these patients. Instead, CEA and calcitonin levels are measured in addition to routine neck ultrasound. For patients diagnosed with MEN 2A or 2B, annual screening should be performed for pheochromocytoma (2A and 2B) and hyperparathyroidism (2A) as well. Patients with detectable serum markers (CEA or calcitonin) should undergo US of the neck and, depending on the level of calcitonin, CT or MRI of the chest, abdomen (with liver protocol) and axial skeleton to detect any recurrence. For those individuals who have elevated serum markers and repeat imaging fails to detect recurrent disease, conservative follow-up with repeat serum measurement of CEA and calcitonin every 6 months should be performed. Anaplastic carcinoma and lymphoma cannot be followed the same way as patients with DTC. Routine physical examinations, neck ultrasound, additional cross-sectional imaging, and measurement of CEA and LDH are therefore utilized.

Disease Recurrence

The risk of recurrence depends largely on tumor biology, extent of initial surgery, and other prognostic variables. Approximately 30% of patients with DTC will develop recurrent disease with 66% of patients recurring within the first decade after definitive treatment. Most recurrences (80%) are isolated to the neck and most commonly involve the cervical lymph nodes in 74% of cases. Other less common sites of recurrence include the thyroid remnant (20%), or tracheal and local muscle (6%). The remaining 20% of patients who recur develop distant metastatic disease, most commonly to the lungs, which is seen in approximately 60% of individuals with distant metastatic disease. Half of the patients with distant metastatic disease will die of their disease.

The goal of a surveillance program is therefore to detect recurrent disease in a timely fashion so that appropriate medical and surgical intervention can be undertaken. The treatment of recurrent disease depends partly on the iodine avidity of the disease as well as the surgical resectability. In patients with recurrent well-differentiated disease (PTC, FTC, Hürthle cell carcinoma) in which stimulated Tg levels are 1 to 10 ng/mL but the disease is nonresectable and nonradioiodine responsive, TSH suppression should be undertaken with levothyroxine. If stimulated Tg levels are >10 ng/mL and all imaging is negative in detecting recurrence, radioiodine ablation should be considered, followed by a postablation radioactive thyroid scan to detect residual disease. In

instances in which the recurrence is detected locoregionally by physical examination or imaging (usually ultrasound or CT), surgical resection is the preferred management option. Reoperation in the thyroid bed is associated with increased risk of RLN injury and potential avascularization of parathyroid glands; therefore, surgical intervention should be individualized. We most often recommend surgery in settings in which recurrent disease is greater than 1 cm, is in an anatomically worrisome location (concern for tracheal or nerve involvement) or continued growth is observed over time. Finally, treatment of distant metastatic disease depends on the site of metastases. Central nervous system (CNS) disease should be considered for neurosurgical resection in select patients or radioiodine ablation and/or image-guided radiation therapy. Bone and distant metastases other than the CNS should be treated surgically in the presence of enlarging lesions, for palliation in symptomatic patients, or for bone metastases involving weight-bearing extremities. External-beam radiation is likewise an option for patients unable to tolerate surgery but with disease that is negative on radioiodine uptake scans. For iodine-avid disease, radioiodine ablation remains an option, but in non–iodine-avid disease which is progressive or symptomatic, referral for clinical trials should be considered.

NEOPLASMS OF THE PARATHYROID GLANDS

Primary Hyperparathyroidism

Although there are many causes for hypercalcemia (Table 17.7), primary hyperparathyroidism (PHPT) is defined as hypercalcemia resulting from the inappropriate, autonomous overproduction of parathyroid hormone (PTH) by one or more parathyroid glands. PHPT is two to three times more common in females than males with approximately 100,000 new cases diagnosed annually in the United States. A solitary parathyroid adenoma is most commonly responsible for PHPT, present in 85% to 90% of patients, and less commonly it is caused by multigland parathyroid hyperplasia (10% to 15%).

TABLE 17.7 Differential Diagnosis of Hypercalcemia

- Primary hyperparathyroidism
  - Solitary adenoma
  - Multigland hyperplasia
  - Multiple gland adenoma
- Secondary/tertiary hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Medication
  - Lithium
  - Hydrochlorothiazide
- Malignancy
  - Parathyroid carcinoma
  - Multiple myeloma
  - Tumors producing PTH-related peptide (ovarian, lung)
  - Acute or chronic leukemia
- Sarcoidosis
- Thyrotoxicosis
- Paget disease
- Increased intake
  - Milk-alkali syndrome
  - Vitamin A toxicity
  - Vitamin D toxicity

Presentation and Diagnosis

The presentation of patients with PHPT has changed over the last several decades with 80% to 85% of patients being asymptomatic and diagnosed on routine laboratory values obtained for other reasons. Patients with asymptomatic PHPT may not be truly asymptomatic as many symptoms of hypercalcemia go unrecognized or are attributed to medical conditions other than PHPT. Nonspecific, constitutional symptoms of decreased energy, sleep disturbance, depression, muscle weakness, and bone/joint pain have all shown improvement when hypercalcemia secondary to PHPT is corrected demonstrating that these symptoms may be the initial, subtle presentation of the disease. Some patients present with more typical symptoms of hypercalcemia, triggering a workup for PHPT. End-organ effects of prolonged hypercalcemia, including nephrolithiasis and osteoporosis are among the more common symptoms prompting a formal evaluation for PHPT, particularly in younger patients. Hypercalcemia may lead to symptoms of increased thirst and polyuria secondary to the inhibitory action of calcium on the antidiuretic hormone, resulting in a state similar to nephrogenic diabetes insipidus. Nephrolithiasis may occur secondary to the effect of PTH increasing renal tubular reabsorption of filtered calcium. Chronic PHPT may cause severe bone demineralization

leading to osteoporosis and fractures. Finally, severe hypercalcemia (>12 mg/dL) has cardiac implications such as shortened QT interval, hypertension (possibly from concomitant renal insufficiency or calcium-mediated vasoconstriction), and deposition of calcium leading to accelerated atherosclerosis as well as alterations in mental status. It is therefore imperative that patients undergo an expeditious workup when elevated or high-normal levels of calcium are discovered with or without the above symptoms.

PHPT is defined as an elevated or high-normal calcium level with an inappropriately nonsuppressed PTH levels. The diagnosis is contingent on the presence of normal renal function and normal to increased urinary calcium excretion. Perhaps the most sensitive and useful test to diagnose PHPT in patients with hypercalcemia is the measurement of serum intact parathyroid hormone (iPTH) levels. This test determines the active or "intact" form of PTH as older tests measured inactive forms of PTH or byproducts of PTH degradation that did not play a role in calcium homeostasis. In patients undergoing evaluation for possible PHPT, measurement of 24-hour urine calcium should be performed to rule out benign familial hypocalciuric hypercalcemia (FHH) which will typically be <100 mg/day with this condition. Finally, in making the diagnosis of PHPT, vitamin D deficiency should be ruled out and corrected if present. A deficiency in vitamin D (usually measured as 25-hydroxyvitamin D) will cause an increase in iPTH, mimicking PHPT. Once the vitamin D level has been corrected with supplementation, repeat calcium and iPTH should be measured to ensure the accurate diagnosis of PHPT. Normocalcemic PHPT is a recently recognized variant that presents with high PTH levels and normal serum calcium levels; it is incompletely characterized at this time with some but not all patients progressing to hypercalcemic PHPT. Once the diagnosis of PHPT has been established, the need for parathyroidectomy should then be established.

Surgical Indications

Surgical removal of the parathyroid gland(s) responsible for autonomous production of PTH is the only effective treatment for patients with PHPT. All patients who have symptomatic PHPT should be referred for parathyroidectomy in order to relieve symptoms and prevent complications of chronic hypercalcemia. This category includes patients with overt nephrolithiasis, recent fractures, osteoporosis or worsening bone mineral

density, bone pain, osteitis fibrosa cystica, pancreatitis, mental status changes, or proximal muscle weakness. Many patients, as discussed earlier, present with asymptomatic disease and the criteria to operate on these individuals have changed over time as decided by an international consortium of experts in the field. Parathyroidectomy is recommended when the serum calcium level is greater than 1 mg/dL above normal as well as for objective evidence of renal involvement, including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria (24-hour urine calcium level >400 mg/dL) with increased stone risk, or impaired renal function (glomerular filtration rate <60 mL/min). Osteoporosis, history of fragility fractures, or evidence of vertebral compression fracture on spine imaging as well as age less than 50 years, are also indications to operate on patients with asymptomatic PHPT.

Preoperative Imaging

Although not useful or recommended to confirm the diagnosis of PHPT, preoperative imaging studies greatly facilitate operative planning and gland localization in suspected single-gland disease. Imaging modalities commonly used include ultrasound, ^{99m}technetium-sestamibi radionuclide scan with or without single photon emission computed tomography (SPECT), and 4D-CT. A nomenclature system has been designed that takes into account the pathologic position of the parathyroid glands and helps radiologists communicate the location of abnormal parathyroid glands with the surgeon (Fig. 17.4).

Although ultrasonography is operator dependent, it is noninvasive, inexpensive, and can be used to evaluate concomitant thyroid pathology. Because of its reliance on the experience of the operator, the positive predictive value is low (50% to 70%) but when combined with sestamibi radionuclide scan can approach 90% and is a useful adjunct for equivocal sestamibi scans. The ^{99m}technetium-sestamibi scan relies on the fact that sestamibi is a lipophilic cation that concentrates in mitochondria. Since parathyroid adenomas and hyperplastic parathyroid glands are metabolically more active when compared to their normal counterparts, the mitochondrial concentration in these glands is higher and sestamibi therefore concentrates in these glands, allowing them to be imaged on radionuclide scan. When combined with SPECT imaging, sestamibi scan can more accurately detect smaller parathyroid glands and those that are more posteriorly located. The use of sestamibi radionuclide scan alone has

a sensitivity of 65% to 90% in detecting parathyroid adenomas or hyperplastic glands. 4D-CT has become increasingly utilized in the localization of parathyroid adenomas. This modality involves CT angiography of the neck using narrow slices with perfusion to the parathyroid glands calculated as perfusion over time. This perfusion is then extrapolated as an indicator of gland function since parathyroid adenomas as hyperplastic glands have higher metabolic activity and thus higher perfusion. The 4D-CT can therefore be used to gain information not only on the location of suspected glands but also their function. Patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging should be performed based on their regional imaging capabilities.

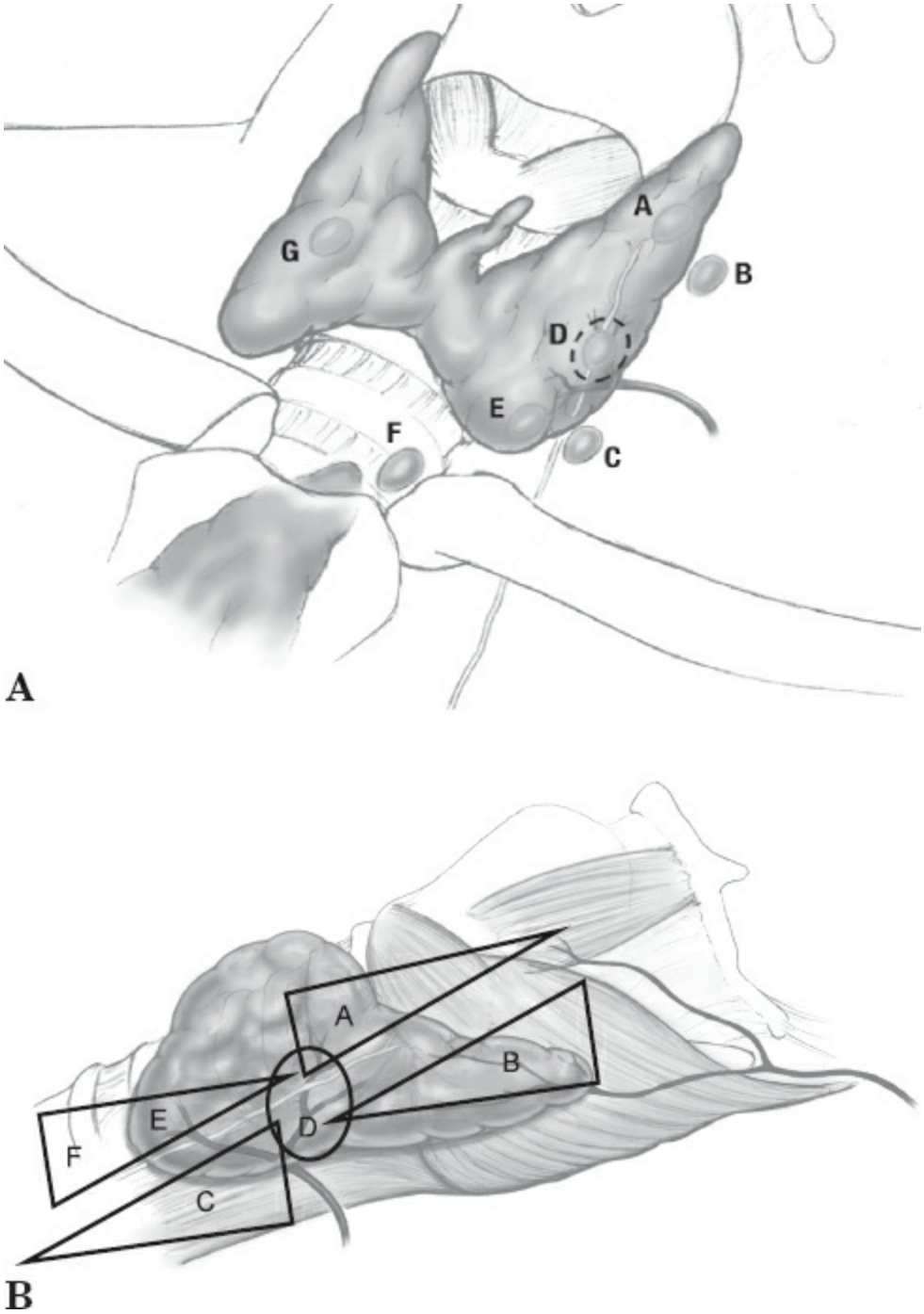


Figure 17.4 **A** and B: Nomenclature system for parathyroid location. In this classification scheme a *type A* gland is a "normal" superior gland in proximity to the posterior surface of the thyroid parenchyma. It may be compressed within the capsule of the thyroid. A *type B* gland is a superior parathyroid gland that has fallen posteriorly into the tracheoesophageal groove. There is minimal or no contact between the gland and the posterior surface of the thyroid tissue. A *type C* gland is a superior gland that has fallen posteriorly into the tracheoesophageal groove and lies at the level of or below the inferior pole of the thyroid. The

type D gland lies in the mid region of the posterior surface of the thyroid parenchyma, near the junction of the RLN and the inferior thyroid artery. The *type D* gland may be either a superior or inferior gland, depending on its exact relationship to the nerve, which generally cannot be determined on imaging. The *type E* gland is an inferior gland in close proximity to the inferior pole of the thyroid parenchyma anterior to the trachea. The *type F* gland is an inferior gland that has descended into the thyrothymic ligament or superior thymus. It may appear to be "ectopic" or within the mediastinum. Finally, the *type G* gland is a rare intrathyroidal parathyroid gland. (Reprinted with permission from Rodgers SE, Hunter GJ, Hamberg LM, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. *Surgery* 2006;140(6):932–940.)

Surgical Technique

In the era of preoperative localization, minimally invasive parathyroidectomy has become the most common surgical treatment for PHPT. A standard cervical exploration involving four-gland evaluation as the primary procedure of choice is now often reserved for patients in whom multigland involvement is suspected prior to surgery (such as MEN1 or 2A) or in cases in which preoperative localization was not possible. The four-gland approach affords the ability to evaluate all four glands and resect as necessary based on the visualized pathology. In cases of four-gland parathyroid hyperplasia causing PHPT, a three- and-a-half-gland parathyroidectomy is performed with preservation of half of the most normal appearing parathyroid gland with its blood supply.

Minimally invasive parathyroidectomy is the most common surgical intervention for PHPT in part because of the high prevalence of a single adenoma as the cause for PHPT (80% to 85% of cases). The technique targets a specific gland and as such relies on accurate preoperative imaging and intraoperative PTH measurement in order to be successful. At MDACC, at the time of operation, a baseline PTH level is drawn and surgical dissection is then directed at the culprit gland identified on preoperative imaging. Five and 10 minutes after the gland is removed, a repeat PTH level is checked and a 50% decline in PTH level from baseline is predictive of cure in 96% of cases. Failure of the PTH to drop by 50%, a rebound of the PTH level, or a level that plateaus above the normal range indicates residual disease and prompts a four-gland exploration. Surgeons

who utilize intraoperative PTH monitoring should use a sampling protocol that is reliable to their local environment and be able to interpret PTH decay dynamics.

Exploration of all four glands is the gold standard surgical approach for patients with PHPT and allows visualization of all glands prior to removal of any abnormal tissue. In experienced hands this approach has a low complication rate with a cure rate over 95%. After appropriate preoperative workup, the patient is brought to the operating room and general endotracheal anesthesia is induced. The patient's neck is extended, often facilitated by a shoulder roll, and placed in the semi-Fowler position with arms tucked at the side for maximum exposure and surgeon access to the field. A transverse incision, utilizing a skin crease for cosmesis, is made approximately 2 cm superior to the sternal notch. Dissection is then carried through the subcutaneous tissue and platysma muscle. The strap muscles are then divided along the median raphe and because statistically most parathyroid adenomas occur in the right inferior position, attention is directed here first. The strap muscles are then elevated off of the posteriorly positioned thyroid gland and the gland is retracted medially. With gentle retraction, the middle thyroid vein is encountered, ligated, and divided in order to allow additional elevation and medial retraction of the thyroid gland. This facilitates exposure of the carotid sheath and structures posterior to the thyroid which are then palpated, prior to any dissection, in order to discover any suspicious parathyroid glands. If no obvious pathology is identified, attention is turned to locating the right inferior gland first. With the thyroid gland rotated medially, the inferior thyroid artery is identified and preserved so as to not devascularize the parathyroid glands. The RLN is then identified and protected as it approaches the inferior thyroid artery. It is anterior to this position that the inferior parathyroid is often located, usually inferior to the thyroid gland in the thyrothymic tract but also possibly residing within the capsule of the lower thyroid pole. After the inferior gland is identified, the superior parathyroid gland is identified by tracing the RLN superiorly as it enters the cricothyroid membrane. The superior gland can usually be found within 1 cm of this location, posterior and lateral to the RLN and thyroid gland. Once both glands are discovered on one side, the contralateral side is explored where the glands are usually in mirror-image position to the previously identified parathyroid glands. Once all four glands have been discovered, the abnormal gland is gently teased from its position, paying

special attention to preserving the RLN, and the gland elevated on its vascular pedicle. The pedicle is then clipped or ligated and the parathyroid gland is removed. In cases where the glands are hyperplastic, attention should first be turned to partial resection of the most normal (smallest), clearly viable gland in order to preserve 50 to 80 mg of tissue. As resection of the other glands proceeds, the viability of the preserved gland should always be checked prior to resecting the next gland as this allows greater freedom in case the gland becomes nonviable. Less frequently, all four glands can be resected and the smallest one placed on ice in order to mince and reimplant approximately 50 to 80 mg of tissue in the sternocleidomastoid or nondominant brachioradialis muscle. The sternocleidomastoid is often chosen because it is already exposed during the procedure. However, some surgeons prefer to reimplant into the brachioradialis because if recurrent hyperparathyroidism occurs it would avoid a repeat operation in the neck. In particular, cases of PHPT thought to be due to hereditary syndromes should have any reimplantation performed in the nondominant forearm, as recurrent hyperplasia is highly likely. In any case, the fibers of the muscles are gently spread so as to retain the blood supply to the muscle and ultimately increase the likelihood of parathyroid gland neovascularization. Care should be taken to avoid a hematoma as this will severely compromise the ability of the parathyroid glands to engraft. The minced parathyroid is then placed within a single muscle pocket and the spread muscle is then gently reapproximated with either Prolene sutures or absorbable suture tagged with hemoclips. The hemoclips or Prolene sutures serve to identify the location of the gland in case reoperative surgery is necessary. Autotransplantation in this manner is successful in 80% of cases.

If preoperative imaging localizes a specific parathyroid gland as suspicious for a solitary adenoma, and intraoperative PTH levels can be measured, then a minimally invasive parathyroidectomy can be performed. Prior neck surgery is not necessarily a contraindication to a minimally invasive approach and may actually be preferred as it allows direct exposure to a solitary adenoma in an otherwise scarred operative field. This technique allows a solitary adenoma to be removed through a modest (2 cm) incision in an outpatient setting. At the time of surgery, the patient is placed into the semi-Fowler position as previously described and a baseline PTH is drawn. The procedure can be performed under general or locoregional anesthesia which may be desirable in older individuals or

those for whom general anesthesia may be hazardous. A 2- to 3-cm incision is then made on the side of the localized adenoma medial to the sternocleidomastoid in line with a traditional Kocher incision. The adenoma is then resected as previously described and a repeat PTH level is drawn 5 and 10 minutes after removal of the gland to ensure a 50% or greater decrease in serum PTH. If the level does not drop, a traditional four-gland exploration should be performed.

A thorough knowledge of parathyroid embryology is required in order to locate pathologic parathyroid glands. The superior parathyroid glands are derived from the fourth branchial pouch along with the thyroid gland. It is for this reason that the superior parathyroid glands do not descend significantly during development and remain closely associated with the posterior aspect of the thyroid gland during development. The inferior parathyroid glands, in contrast, are derived from the third branchial pouch, as is the thymus gland. As the inferior glands descend, they can be found anywhere along the thyrothymic tract (base of the skull to the anterior mediastinum), often in close association or embedded within the thymus gland.

The parathyroid location nomenclature system (Fig. 17.4) takes into account the embryologic migration of the glands and assists in locating glands. When a gland cannot be located, a systematic approach with knowledge of embryology must be utilized in order to locate the gland. If a superior gland cannot be located, attention should be turned to the cricothyroid membrane where the vast majority of superior parathyroids are located within 1 cm of this position. The posterior thyroid should be reinspected as the gland is often located under a fascial covering that once released will reveal the “missing” gland. The superior thyroid artery may be sacrificed in order to obtain better medial rotation of the thyroid gland and improved exposure of its posterior surface. If the gland cannot be located despite interrogating the posterior lateral aspect of the thyroid gland, the tracheoesophageal groove is then inspected, including posterior to the esophagus and subsequently following this into the upper mediastinum if necessary.

Rarely are superior parathyroid glands located intrathyroidal and so hemithyroidectomy is seldom indicated. Additionally, intrathyroidal parathyroid glands are often seen on preoperative ultrasound, and aspirations sent for PTH can confirm this as a possible location prior to surgical exploration. Finally, the carotid sheath should be opened and

inspected for the presence of a missing gland. If an inferior parathyroid gland cannot be located, the posterior lateral border of the thyroid gland is inspected from the inferior border to above the junction where the RLN and inferior thyroid artery crosses each other. Because inferior parathyroid glands can be located in close association with the thyroid gland, the anterolateral surface of the thyroid is palpated to discover any suspicious areas and the overlying fascia divided to allow exposure to such a gland. It is in these situations that intraoperative ultrasound may be useful in order to identify a parathyroid gland that is situated deeper in the thyroid parenchyma. In these cases a limited thyroidotomy can be performed to remove the gland. If these locations do not reveal the inferior parathyroid gland, a cervical thymectomy should be performed as upward of 17% of inferior glands can be found in the thymus. This is a relatively simple maneuver that adds little time to the operative procedure. In the vast majority of instances, the “missing” gland is located in its normal anatomic position on reexploration.

Parathyroid Carcinoma

Although parathyroid carcinoma is a cause of PHPT, with calcium levels often greater than 14 mg/dL (compared to 10 to 11 mg/dL in benign PHPT), it is rare and occurs in only 0.1% to 4% of cases. The incidence is equal among men and women with presentation usually occurring in the fifth decade. No true risk factors have been elucidated, likely due to the rarity of the disease. An association has been made between chronic renal failure and dialysis, thought to be due to malignant transformation of chronically hyperplastic glands. Associations have also been made with MEN syndromes (1 and 2A) and external-beam radiation but there is no definitive proof of this relationship. There is, however, an increased prevalence of parathyroid carcinoma in patients with hyperparathyroidism-jaw tumor syndrome. These patients most commonly have a germline mutation in the HRPT2/CDC73 gene whose product, parafibromin, is thought to regulate RNA polymerase-II–mediated transcription and histone methylation for certain genes. The exact role of this gene product is not yet understood. Various inactivating mutations in the tumor suppressor gene, HRPT2/CDC73, have been found in the majority of patients with sporadic parathyroid carcinoma but much research is still needed in this particular field.

The vast majority (95%) of parathyroid carcinomas are functional and as

such, these patients present with severe signs and symptoms of hypercalcemia. In contrast to benign causes of PHPT, the PTH level of patients with parathyroid carcinoma is often five times the upper limit of normal with calcium levels greater than 14 mg/dL. In contrast to patients with benign PHPT in which 80% of cases are asymptomatic, only 20% of patients with parathyroid carcinoma are asymptomatic. It is the extreme levels of hypercalcemia that results in renal and skeletal symptoms in 60% and 50% of patients, respectively. These high levels more commonly cause symptoms of polyuria, polydipsia, nocturia, bone pain/fractures, nephrolithiasis, renal dysfunction, and pancreatitis when compared to benign PHPT where calcium levels are only mildly elevated. A significant number of patients (40%) with parathyroid carcinoma will present with a palpable neck mass and the diagnosis should therefore be entertained anytime a patient with PHPT presents with such a mass. Although hoarseness may be present, invasion of the RLN by a parathyroid cancer is actually infrequent, occurring 10% of the time.

Diagnosis and Treatment

Diagnosis of parathyroid carcinoma is suspected in patients diagnosed with PHPT as previously described but have significantly elevated calcium levels (>14 mg/dL) and/or a palpable neck mass. Preoperative FNA is contraindicated in these situations for risk of local tumor dissemination. It is extremely difficult to diagnose parathyroid cancer with an FNA biopsy and requires clinical examination of the gland intraoperatively or permanent pathologic sectioning to determine malignancy. Preoperative imaging can provide insight into the malignant potential as preoperative ultrasound or 4D-CT may identify a gland with irregular margins or local invasion. Once the diagnosis of PHPT has been established and parathyroid carcinoma suspected, the patient is brought to the operating room and an en bloc resection of the parathyroid gland with avoidance of capsular disruption should be performed; this may involve en bloc resection of adherent tissues including the ipsilateral thyroid lobe, ipsilateral central compartment lymph nodes and removal of ipsilateral tracheoesophageal soft tissue. If the tumor is adherent to the strap muscles, RLN, or esophageal wall, they should be removed en bloc with the tumor. In cases where parathyroid cancer is not suspected preoperatively or preoperative imaging does not indicate signs of malignancy, parathyroid carcinoma should be suspected intraoperatively if the gland is adherent to

surrounding structures, appears gray and firm in nature, or palpable lymph nodes are present. In these cases an en bloc resection should be performed as described. Histologic diagnosis on final pathology relies on identification of unequivocal angioinvasion; additionally, biomarkers may be helpful. Patients diagnosed with parathyroid carcinoma should undergo regular surveillance with serum calcium and PTH levels; those with elevations in these markers should raise suspicion for possible regional recurrence or distant metastatic disease.

The 8th edition of AJCC guidelines has established a staging system for parathyroid carcinoma (Table 17.8). The extent of surgery, with en bloc resection of the tumor, has been shown to correlate with improved overall and disease-free survival in multivariate analysis. Because of the rarity of this disease, accumulation of accurate survival data is difficult but suggests a 5-year survival of approximately 75% to 85% and 10-year survival of 50% to 75%. Local recurrence occurs in 25% to 80% of individuals at varying time periods from the initial surgery but typically occurs 2 to 4 years after surgery. Distant metastases, most commonly to the lungs, bone, liver, or pancreas, occur in 25% of patients.

Adjuvant external-beam radiation is not routinely recommended for treatment of parathyroid carcinoma, instead it is often reserved for palliation. Chemotherapy has not shown a survival benefit in patients with parathyroid carcinoma despite short-lived responses to single-agent dacarbazine or in combination with cyclophosphamide and fluorouracil for metastatic disease. Our institutional management of this disease and the clinical outcomes of these patients have not demonstrably changed over the last five decades, highlighting the need for oncologic improvement.

In patients with suspected recurrent disease, either locally or distant, imaging should be performed to identify the site and extent of disease with a sestamibi and CT scan. Recurrent hypercalcemia is often the first sign of tumor progression. Reoperative surgery can be undertaken with the knowledge that a cure is unlikely but that symptoms of hypercalcemia can be improved in 70% to 85% of patients. The risk of reoperative neck surgery must be balanced with the ability to palliate the symptoms of hypercalcemia in a patient. A solitary focus of metastatic disease can be resected with the patient’s understanding that this effort has not been shown to improve survival, only to improve symptoms. There is no benefit to partial resection of widely metastatic disease and these patients should be referred for medical treatment of their hypercalcemia which represents

the main cause of morbidity and death in patients with recurrent parathyroid cancer.

TABLE 17.8 AJCC Staging System for Parathyroid Cancer

Definition of Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Atypical parathyroid neoplasm (neoplasm of uncertain malignant potential)
T1	Localized to the parathyroid gland with extension limited to soft tissue
T2	Direct invasion into the thyroid gland
T3	Direct invasion into recurrent laryngeal nerve, esophagus, trachea, skeletal muscle, adjacent lymph nodes, or thymus
T4	Direct invasion into major blood vessel or spine
Definition off Regional Lymph Node (N)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/ Delphian lymph nodes) or superior mediastinal lymph nodes (level VII)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (level I, II, III, or V) or retropharyngeal nodes
Definition of Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Adapted from the *AJCC Cancer Staging Manual*, 8th edition.

The treatment of malignant hypercalcemia is particularly important in patients with disseminated disease or in patients with negative localization studies in which surgery is not an option. In the acute setting, large volume intravenous fluid resuscitation is instituted with addition of a loop diuretic to increase renal calcium clearance. Agents such as mithramycin and calcitonin have proved to be effective but are limited by either toxicity or short duration of action. While not feasible in the chronic setting, intravenous infusion of bisphosphonates (pamidronate or zoledronic acid) have resulted in variable responses that may last for several weeks in some patients. Calcimimetic agents have proved to be the most effective agents for the long-term treatment of hypercalcemia secondary to parathyroid carcinoma. Cinacalcet is approved for the treatment of hypercalcemia

secondary to inoperable parathyroid cancer based on a single-armed trial of the agent.

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18 Hematologic Malignancies and Splenic Tumors

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INTRODUCTION

Patients with hematologic malignancies represent an interesting and often challenging cancer population for the surgical oncologist. Whether to perform an excisional biopsy for a patient with suspicion of lymphoma or a therapeutic splenectomy in a patient with a hematologic malignancy, surgeons in cancer centers are frequently involved in the care of these individuals. Therefore, it is important for surgical oncologists to be familiar with these malignancies and the indications for appropriate interventions. The treatment plan almost always involves the participation of our medical oncology colleagues and a multidisciplinary approach.

Hematologic disorders are categorized based on the cell type of origin. This chapter will review hematologic malignancies and splenic tumors as they relate to the role of a clinical surgical oncologist and describe the therapeutic interventions necessary from a surgeon's perspective.

Leukemia, lymphoma, and myeloma account for 10% of new cancer diagnoses in the United States. An estimated 171,550 people were diagnosed with one of these hematologic malignancies in 2016 and approximately 58,320 people will die of these diseases. Leukemia is the most common malignancy in children and adults younger than 20 years, whereas non-Hodgkin lymphoma (NHL) is the third most common cancer in the same population. For patients less than 35 years of age, acute leukemia is the leading cause of cancer deaths.

THE LEUKEMIAS

Polycythemia Vera and Essential Thrombocythemia

Polycythemia vera is characterized by an autonomous expansion of red blood cell mass and volume with a variable effect on white blood cells and platelets. The etiology is believed to involve a red blood cell clone highly

sensitive to erythropoietin. Approximately three-fourths of patients with polycythemia vera develop palpable splenomegaly and half develop hepatomegaly. Essential thrombocythemia is associated with an increase in megakaryocytes and platelet count with a variable effect on erythrocytes and white blood cells. Increased risk of thrombosis and hemorrhage occur in both polycythemia vera and essential thrombocythemia.

The primary treatment for both diseases is phlebotomy, low-dose chemotherapy, or the combination of these approaches. The goal of treatment is to maintain a hematocrit less than 45% in men and 42% in women. Splenectomy has little to no role in the treatment of most patients with polycythemia vera or essential thrombocythemia. Although splenectomy has a minimal role in the treatment of these illnesses, a condition similar to myelogenous metaplasia develops in a few patients who then require splenectomy. The operative risks are greater and the survival is poorer in this group than in patients with myelogenous metaplasia. Patients with polycythemia vera or essential thrombocythemia should be treated with aggressive nonoperative therapy and offered splenectomy only when pain or when anemia and thrombocytopenia are refractory to other treatments. Splenectomy does not increase the survival rate, but it may improve the quality of life.

Myelogenous Metaplasia

Myelogenous metaplasia is a chronic myeloproliferative disease where immature myeloid precursor cells settle in the reticuloendothelial organs, primarily the spleen, liver, and lymph nodes. It is characterized by fibrosis of the bone marrow and extramedullary hematopoiesis, resulting in massive splenomegaly in approximately 75% of patients. Some patients are asymptomatic, however, most present with fatigue, anorexia, or weight loss in addition to symptomatic splenomegaly. Either thrombocytopenia or thrombocytosis can occur. Active splenic destruction may be humorally or cellularly mediated. Bone marrow biopsy is necessary for diagnosis. Large platelets, nucleated red cells, anisocytosis, and immature myelogenous elements are often seen on peripheral blood smears.

Initial nonoperative management includes transfusions, steroids, androgens, cytotoxic chemotherapy, and splenic irradiation. Hypersplenism refractory to these primary treatments may warrant splenectomy, however operative mortality is approximately 9%. Nearly a quarter of patients may experience postsplenectomy thrombocytosis and

progressive hepatomegaly. At MD Anderson Cancer Center, the indications for splenectomy in patients with myelogenous metaplasia with myelofibrosis are: (a) severe anemia due to hypersplenism not responding to medical management; (b) chronically symptomatic splenomegaly; or (c) worsening congestive heart failure due to shunting through the spleen. Prior to splenectomy, adequate bone marrow activity must be documented by bone marrow biopsy and nuclear medicine bone marrow scan. If the major site of hematopoiesis is the spleen, a splenectomy may cause severe pancytopenia in these patients. Coagulation studies should also be performed preoperatively.

Postoperatively, these patients are at increased risk for portal vein thrombosis and thrombocytosis. The Mayo Clinic has published a 30-year review of their splenectomy experience with myeloid metaplasia that suggested that postoperative thrombotic complications may be reduced with the use of platelet-lowering therapy. In this study, platelet-lowering therapy consisted of medical therapy with hydroxyurea, aspirin, or anagrelide, and platelet apheresis for platelet counts greater than one million. Postoperative portal vein thrombosis may present as a postoperative ileus, hepatic insufficiency, vague abdominal pain, or new-onset ascites. The treatment is 6 months of anticoagulation therapy while collateral circulation develops. To minimize the risk of portal vein thrombosis, the authors recommend ligating the splenic vein at its confluence with the superior mesenteric vein to maintain laminar blood flow.

Once again, splenectomy may improve the quality of life for these patients but does not provide a survival benefit. Following splenectomy, the response rates for anemia are 75% to 95%. For those patients that are poor candidates for surgery, low-dose radiation to the spleen may be used.

Chronic Myelogenous Leukemia

Also known as chronic granulocytic leukemia, chronic myelogenous leukemia (CML) involves the clonal proliferation of myelogenous stem cells. Ninety percent of CML patients have the Philadelphia chromosome, which is the characteristic translocation of chromosomes 9 and 22. Treatment response may be measured using PCR levels of the Philadelphia chromosome.

CML has a chronic benign phase, an accelerated phase, and an acute blastic transformation (i.e., blast crisis). Most patients present with

symptoms of the chronic phase, which include fatigue, weakness, night sweats, low-grade fever, and abdominal pain. On physical examination, splenomegaly may be an isolated finding. Anemia or thrombocytopenia may result from hypersplenism. The median duration of the chronic phase is about 45 months and patients should be followed every 3 to 6 months. Approximately 80% of patients with CML will progress from the chronic phase to the acute leukemic phase.

The acute blastic phase may present as progressive fatigue, high fevers, symptomatic splenomegaly, anemia, thrombocytopenia, basophilia, and bone or joint pain. Frequent infections and bleeding episodes may manifest with increased splenic destruction of blood components. Traditional treatments of CML include tyrosine kinase inhibitors (e.g., imatinib), conventional chemotherapy with hydroxyurea or busulfan, and bone marrow transplant. Tyrosine kinase inhibitors are often the initial treatment choice for most newly diagnosed patients with CML.

The indications for splenectomy in CML are to relieve the symptoms of splenomegaly or reduce the need for transfusions. In the rare occasion where medical management fails, our experience with splenectomy for patients in accelerated or blastic phase CML at MD Anderson demonstrates that splenectomy can be performed safely during this phase and thrombocytopenia can be reliably reversed.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is characterized as a low-grade neoplastic disorder involving the accumulation of mature appearing but functionally incompetent B cells. It is the most common leukemia in the Western Hemisphere, and the median age of onset is in the seventh decade of life. Splenomegaly is common in the advanced stages of the disease. Common symptoms of hypersplenism include abdominal pressure, pain, gastric compression, anemia, or thrombocytopenia. Second malignancies develop in 20% of these patients, most commonly lung cancer, melanoma, or sarcoma. Overall survival is between 1 and 20 years, representing a wide range of indolent to aggressive disease courses. The most common cause of death in patients with CLL is infection from progressive immune system compromise.

The Rai Classification system is employed in CLL (Table 18.1). Multiple randomized controlled trials have failed to demonstrate a long-term survival benefit with immediate versus delayed therapy for early-

stage asymptomatic CLL. Accordingly, treatment is reserved for patients who develop disease-related symptoms or progressive disease (i.e., "active disease"). Treatment options include purine analogs (e.g., fludarabine), alkylating agents (e.g., chlorambucil), monoclonal antibodies (e.g., rituximab) or ibrutinib, as single agents or in combination. Splenectomy may be recommended for patients refractory to chemotherapy or with symptomatic splenomegaly. Splenectomy has been shown to improve thrombocytopenia in 70% to 80% and anemia in 60% to 70% of patients with CLL. Our experience at MD Anderson demonstrates that splenectomy provides an excellent hematologic response in patients with either isolated anemia or thrombocytopenia, but a poor response in patients with both. This suggests that hematopoietic reserve is necessary for a significant clinical response to splenectomy. In selected subgroups of patients with advanced-stage CLL, splenectomy demonstrates a significant survival advantage compared with conventional chemotherapy. This selected subgroup of CLL patients includes those with either hemoglobin levels ≤10 g/dL or platelet count ≤50 × 10^9 L.

TABLE 18.1 Rai Staging of Chronic Lymphocytic Leukemia

Stage	Criteria
0	Lymphocytosis (WBCs >15,000/mL with >40% lymphocytes in the bone marrow)
I	Lymphocytosis with lymphadenopathy
II	Lymphocytosis with enlarged liver or spleen (lymphadenopathy not necessarily present)
III	Lymphocytosis with anemia. Anemia may be due to hemolysis or due to decreased production (lymphadenopathy or hepatosplenomegaly need not be present)
IV	Lymphocytosis with thrombocytopenia (platelet count <100,000/μL), anemia, and lymphadenopathy

WBC, white blood cell.

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a monoclonal lymphoproliferative disorder of mature B cells characterized by the pathognomonic cytoplasmic projections that invade the bone marrow and spleen. It is considered a low-grade leukemic disorder that comprises only 2% to 5% of all leukemias

with a 3:1 male predominance typically older than the age of 50 years.

Approximately 10% of HCL patients will have mild symptoms and do not require treatment. Splenomegaly is almost universally present; other symptoms may include weakness and fatigue. Indications for treatment include neutropenia, splenomegaly, hypersplenism, or bone marrow failure. The most common cause of death is infection in the setting of neutropenia.

Prior to the development of effective chemotherapeutic agents, splenectomy was the traditional treatment of choice for HCL patients and was associated with an increased survival. However, since the discovery of more effective systemic agents, splenectomy is no longer routinely performed in this setting. Pentostatin and cladribine result in complete response rates of 80% to 90% which are also more durable responses compared to splenectomy. Splenectomy may be considered in rare cases of the pure splenic form of disease or for palliation in HCL patients refractory to medical management.

Acute Lymphocytic Leukemia and Acute Myelogenous Leukemia

In general, there is no role for splenectomy in the treatment of acute lymphocytic leukemia or acute myelogenous leukemia during induction chemotherapy or relapse. Rare exceptions for splenectomy in these patients include cases of splenic rupture or persistent fungal granulomas of the spleen in patients in complete remission.

Splenic Rupture in Leukemia

Splenic rupture is a rare event in patients with leukemia and is almost exclusively the result of a traumatic injury. This is not due to the leukemia but rather the result of splenomegaly. The incidence of splenic rupture in leukemic patients is 0.2% and comprises 3.5% of all cases of spontaneous splenic rupture.

Patients most frequently present with abdominal tenderness, rigidity, and tachycardia. A chest radiograph may demonstrate an elevated hemidiaphragm or pleural effusion. An abdominal computed tomography (CT) with intravenous contrast is the diagnostic imaging study of choice. Radiographic findings consist of perisplenic and free peritoneal fluid with possible active extravasation of contrast adjacent to a splenic capsular or

hilar injury. For patients who are hemodynamically unstable in the setting of splenic rupture, emergent splenectomy is necessary. For those patients who are hemodynamically stable with evidence of active extravasation of intravenous contrast, emergent arterial embolization by interventional radiology frequently stops further hemorrhage and avoids operative intervention. In evaluating any patient with known splenomegaly and abdominal pain, a clinician must maintain a high index of suspicion for a splenic rupture. Leukemic patients that survive splenectomy after rupture maintain a similar life expectancy as other patients with the same type of leukemia.

THE LYMPHOMAS

Hodgkin Disease

Over the past 25 years, the overall survival of patients with Hodgkin disease (HD) has improved significantly. As our understanding of this tumor biology has improved, so has the use of multiple chemotherapy agents and radiation therapy to treat HD. The role of staging laparotomy has become of historical interest in these patients. The procedure involves liver biopsy, splenectomy, sampling from the periaortic, mesenteric, hepatoduodenal, splenic lymph nodes, as well as any enlarged or abnormal appearing lymph nodes. Adequate staging information is currently based on physical examination and cross-sectional imaging using chest, abdomen, and pelvic CT.

HD is characterized by the presence of multinucleated Reed–Sternberg cells or a variant of these cells. In contrast to NHL in which the predominant cells are malignant lymphocytes, the inflammatory cells outnumber the malignant cell population in HD. The initial symptoms of HD are typically nontender lymphadenopathy, most commonly in the cervical lymph node basins. The axillary, inguinal, mediastinal, and retroperitoneal lymph nodes are less frequently involved at presentation. The presence of B symptoms should also be identified. These include unexplained fever with temperature >38°C, night sweats, or weight loss of >10% body weight over 6 months.

The initial evaluation includes a comprehensive physical examination focusing on all lymph node basins and palpation for hepatomegaly and splenomegaly. Laboratory workup should include a complete blood count with differential and liver function tests. CT of the chest, abdomen, and

pelvis and bone marrow biopsy are performed to determine the extent of the disease. To confirm the suspected diagnosis of HD, core needle biopsy may be used. In cases where the diagnosis remains unclear, excisional biopsy of suspected lymph node involvement may be necessary. For a surgical oncologist, targeting an enlarged lymph node for excisional biopsy that is relatively accessible is the preferred strategy and lends itself to the lowest possible morbidity.

The prognosis of HD depends on the histologic subtype, stage of disease, and response to therapy. The World Health Organization classification of HD identifies four histologic subtypes divided into two main groups: nodular lymphocyte predominant and classical HD, which itself has four categories—nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich.

The Ann Arbor staging system (Table 18.2) was developed in 1971 and used to stage HD based on the extent of disease. Clinical staging includes data from the history, physical examination, and nonoperative diagnostic studies. Pathologic staging historically involved tissue analysis from staging laparotomy. The stages are subclassified to reflect lymphatic disease and extranodal involvement, E; and splenic involvement, S. The presence of systemic symptoms, B, further subclassifies patients with HD.

TABLE 18.2 Ann Arbor Staging System for Hodgkin Disease

Stage	Criteria
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or of an extralymphatic organ and its adjoining lymph node site (IIE)
III	Involvement of lymph node sites on both sides of the diaphragm (III) or localized involvement of an extralymphatic site (IIIE), spleen (IIIS), or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement
A	Asymptomatic
B	Fever, night sweats, or weight loss of more than 10%

Staging laparotomy was initially performed in the setting of all patients

with HD to define the extent of disease. Over the years, laparotomy was used to determine early-stage disease, which could benefit from radiation versus those with extensive disease requiring systemic chemotherapy. A combination of improved noninvasive imaging modalities and more aggressive use of early systemic treatment and radiation therapy have virtually eliminated the role for staging laparotomy for this disease process. At the MD Anderson Cancer Center, nonoperative staging and prognostic factors are used to guide therapy in these patients. This approach is supported by data failing to demonstrate a significant survival advantage between clinical and surgical staging. Performing an invasive staging laparotomy or laparoscopy therefore provides no benefit to HD patients and may delay the initiation of systemic chemotherapy.

The role for splenectomy, however, does occasionally exist in the HD population for two indications. The first is symptomatic splenomegaly. Second are hematologic disturbances such as thrombocytopenia and leukopenia that may result in chemotherapy delays.

Non-Hodgkin Lymphoma

NHL is the most common type of lymphoma and is characterized by the monoclonal proliferation of lymphocytes. Approximately 80% of NHL is derived from B-cell origin and the remaining 20% are from T cells. B-cell NHL is diagnosed and classified into subsets based on the identification of histopathologic markers using monoclonal antibodies and cellular morphology. These criteria for diagnosis depend on diffuse versus follicular (nodular) pattern of lymph node involvement, small versus large cell type, cell surface marker expression, and molecular/cytogenetic findings. Using these differences and others, patients with NHL may be placed into three categories that include mature B-cell, mature T and NK cell, and immunodeficiency-associated lymphomas.

Patients with NHL present with superficial nontender lymphadenopathy, most commonly in the cervical lymph nodes. The Ann Arbor Staging System initially developed for HD was adopted for the staging of NHL. It is generally less helpful for NHL because greater than half of NHL patients present with stage III or higher disease and 20% have B symptoms. Hematogenous spread versus lymphatic spread is more common in NHL compared to HD.

Surgical oncologists may be asked to evaluate patients with NHL for a variety of reasons. These include performing a diagnostic biopsy,

providing vascular access for chemotherapy or rarely, splenectomy. Staging laparotomy is not indicated for NHL. Splenectomy is indicated for NHL patients with symptomatic splenomegaly or pancytopenia requiring frequent transfusion requirements as a result of hypersplenism. NHL patients with a persistent isolated splenic focus of disease may also benefit from splenectomy. The prognosis of these selected individuals is similar to other stage I patients.

Diagnostic Biopsy for Lymphoma

The pathologic diagnosis for a suspected lymphoma relies on appropriate planning and communication between the medical oncologist, surgical oncologist, and pathologist. Surgeons are most often involved with excisional lymph node biopsies when core needle biopsies are nondiagnostic or when having nodal architecture will change management. Roughly 21% of lymph node biopsies will yield lymphoma. A large systematic review revealed that combined fine needle aspiration biopsy and core needle biopsy was able to identify subtypes of lymphoma 66% to 74% of the time; however, it concluded that excisional lymph node biopsy was needed in 25% to 35% of cases in order to fully classify the lymphomas for treatment. Feasibility of excisional lymph node biopsy, however, depends on several factors in order to increase the chances of successful diagnosis.

Imaging plays a role in guiding excisional lymph node biopsy, and PET-CT has an evolving role in the management of lymphoma. It has been used to not only stage patients, but to also provide information of post treatment effect and prognosis after chemotherapy and stem cell transplant. Most patients will present for surgical evaluation after having a PET-CT suspicious for active or residual disease. This combined anatomic and metabolic study is very useful in planning strategies for excisional lymph node biopsies. Lymph nodes can be divided into peripheral and central locations, and strategies for biopsy vary by location. The targeted lymph node for excisional biopsy should be the largest node found on physical examination. Lymph nodes larger than 2 cm have the best diagnostic yield whereas nodes less than 1 cm are unlikely to provide a specific diagnosis. If multiple enlarged lymph nodes are present, the preferential biopsy sites are cervical lymph nodes, then axillary lymph nodes, followed by inguinal lymph nodes. For cases of matted lymph nodes or extranodal disease, a generous biopsy sample is helpful for diagnosis. The fundamental

principle in making the pathologic diagnosis is preservation of architecture; therefore, sharp dissection is preferred over electrocautery.

Peripheral lymph nodes are located in the cervical, supraclavicular, axillary, and inguinal regions. Historical studies have found that the cervical and supraclavicular region have the highest diagnostic yield, and that the axillary and inguinal regions have the lowest. However, in the era of PET-CT and improvements in image-guided biopsy, this result has not been reproduced. In general, peripheral lymph nodes are accessible with minimal dissection and most surgeons are familiar with the anatomy in these regions given their experience with techniques for sentinel lymph node biopsy from breast and melanoma surgery. At present, no radiotracers, dyes, or fluorescence techniques exist to guide dissection in hematologic malignancy, and palpability of the node is the primary clue to guide dissection. Intraoperative ultrasound is a useful adjunct to locate the node in horizontal and vertical planes in order to guide incision placement and limit unnecessary dissection. Limited dissection is important in this patient population as they are often neutropenic and prone to impaired healing and infection. Once dissected, the lymph node should immediately be sent fresh and sterile for appropriate studies (touch prep and flow cytometry). Thus having a pathologist readily available is important. It should be clearly communicated to the pathologist that the biopsy is for a suspected lymphoma to further aid in the appropriate processing of the tissue. Needle biopsies may be helpful to rule out a carcinoma or sarcoma or to provide evidence for a suspected relapse of lymphoma; however, they tend not to be as helpful for the initial diagnosis of lymphoma since the histologic architecture is not preserved.

Central lymph nodes are located in the mediastinum, retroperitoneum, and mesentery. These locations are less amenable to surgical biopsy and core needle biopsies through IR or endoscopy should be utilized before proceeding with surgery. The mediastinum is accessible through mediastinoscopy and should be performed by those familiar with this technique. The retroperitoneum can be accessed through the abdomen or through a retroperitoneoscopic approach in the same manner as retroperitoneal adrenalectomy.

The mesentery can be accessed through laparoscopic techniques, and several case series have been published describing this technique. The mesentery can be accessed with a 5-port technique (1 port in each quadrant, 1 umbilical camera site). The omentum is first reflected cephalad

and tucked under the liver to reveal the colonic mesentery. The small bowel is then run from the ligament of Treitz to the terminal ileum. Obvious lymphadenopathy is carefully excised with sharp dissection and electrocautery, and the area of dissection is marked with clips. No large studies exist regarding laparoscopic lymph node biopsy, however multiple smaller case series describe few complications and no mortalities. The primary morbidity is conversion to an open procedure as there is lack of tactile feedback with minimally invasive techniques. The rate of conversion to open laparotomy ranges from 6% to 33%, and limited information exists regarding the diagnostic sensitivity of laparoscopic biopsy with one study citing a false-negative rate of 6%.

Complications from excisional lymph node biopsy for hematologic malignancy are not well characterized. As many of the procedures for peripheral lymph node biopsy are similar to techniques for sentinel lymph node biopsy for breast and melanoma, risks similar to those seen with sentinel lymph node biopsy (lymphedema, lymphocele, vascular and nerve injury, and wound infection) likely apply. Central lymph node biopsy complications are not well characterized. Additionally, most lymph nodes are located near major vascular structures and care needs to be taken not to cause major bleeding.

MISCELLANEOUS SPLENIC TUMORS

Splenic Cysts

Splenic cysts are typically classified as either primary (true) or secondary (false or pseudocysts) based on the presence of an epithelial lining. Primary cysts may be further classified as parasitic and nonparasitic. Nonparasitic cysts comprise 75% of splenic cysts in the United States and include both congenital and neoplastic cysts. Congenital cysts are characterized as epidermoid or dermoid cysts. These are usually diagnosed in children and young adults. Approximately 90% of nonparasitic true cysts are epidermoid cysts. Neoplastic cysts include lymphangiomas and cavernous hemangiomas. Parasitic cysts are very rare in the United States and are most commonly the result of an echinococcal infection. Secondary cysts are more common than primary cysts and are generally believed to be the result of splenic injury and hematoma formation. Pseudocysts may also develop after acute pancreatitis, infections, or splenic infarcts. Patients with splenic cysts often present with vague symptoms of left upper

quadrant pain and early satiety. Splenic cysts are often detected on physical examination as a palpable mass or incidentally on CT imaging. For nonparasitic splenic cysts <5 cm, conservative management with ultrasound follow-up is recommended. Indications for surgical management for patients with splenic cysts include size >5 cm, symptoms, hemorrhage, infection, or cyst perforation. The surgical options include complete or partial splenectomy, unroofing or marsupialization of the cyst, and fenestration. These can be performed through an open incision, hand-assisted or completely laparoscopic techniques. Percutaneous drainage of splenic cysts is generally avoided due to the high incidence of recurrence and difficulty with subsequent operations due to the resulting inflammatory scarring.

Inflammatory Pseudotumor

Inflammatory pseudotumor, also known as plasma cell granuloma, has features of inflammation and mesenchymal repair. These pseudotumors may be found throughout the body, including the respiratory and gastrointestinal tracts, orbit, and lymph nodes. Similar to pseudocysts, they are believed to result from prior trauma or infection. These lesions are often mistaken for lymphoma, therefore requiring tissue diagnosis with immunohistochemical stains and flow cytometry to differentiate them from lymphoproliferative diseases.

Nonlymphoid Tumors

Nonlymphoid tumors of the spleen may be either benign or malignant. The most common malignant nonlymphoid tumors of the spleen are angiosarcomas, with a worldwide incidence of 0.14 to 0.25/million persons. These tumors tend to have an aggressive biology allowing them to grow quickly and metastasize early in their clinical course. The liver, lung, lymph nodes, and gastrointestinal tract are typical sites of metastasis. Angiosarcomas are associated with exposure to thorium dioxide, vinyl chloride, and arsenic. Splenectomy is indicated in these patients but is rarely curative. The overall prognosis is poor, with a median survival of only 5 months. Other rare malignant nonlymphoid splenic tumors include Kaposi sarcoma, malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma, plasmacytomas, hemangiosarcomas, and lymphangiosarcomas.

Splenic Metastases

Splenic metastases are rare events despite the large amount of total blood flow to the spleen. This may be related to the immunologic function of the spleen and its ability to clear microscopic metastatic disease. When metastases occur, they are usually associated with disseminated disease. The incidence of splenic metastases in autopsy studies ranges from 1.6% to 30%. The most frequently detected metastases originate from melanoma, breast, and lung cancer. Other primary sites include ovarian, endometrial, gastric, colonic, and prostate cancers. Splenectomy may be considered for solitary metastases with stable or treated primary disease such as melanoma or as part of a debulking procedure for ovarian, primary peritoneal, or appendiceal cancers. Other possible indications for splenectomy for metastatic disease include the treatment of complications of perforation of adjacent viscera, hemorrhage, or splenic vein thrombosis.

SPLENECTOMY

Splenectomy for Hypersplenism

Anemia, neutropenia, and thrombocytopenia may occur for a number of reasons in patients with hematologic malignancies. Because only patients with excessive destruction of a blood component will benefit from a splenectomy, a careful workup should be done to identify the etiology of the process. Patients with hypersplenism may present with a normal-sized spleen, and others may have massive splenomegaly without hypersplenism.

Infusion of the patient's or normal donor platelets tagged with ^{111}indium is helpful in determining whether the spleen is the site of destruction. Patients with an acquired hemolytic anemia generally have a positive Coombs test, and the detection of the warm antibody is a good indication that splenectomy will be beneficial. Although chromium-labeled red blood cell scans may be useful in demonstrating decreases in red blood cell survival, they are not as helpful in identifying the site of sequestration. In cases of suspected splenic sequestration, a bone marrow biopsy is important to determine whether adequate precursor cells are available or whether the patient depends on the hematopoietic activity of the spleen.

Splenectomy in patients with CML has been associated with severe bleeding problems. These may be related to impaired clot formation caused by proteases and serases produced by granulocytes. Patients with

CML and severe leukocytosis should receive chemotherapy in an attempt to decrease the WBC count to approximately 20,000 cells/mL. Experience at MD Anderson suggests that splenectomy is best avoided in patients with CML in whom WBC counts cannot be controlled with chemotherapy. Splenectomy should also be avoided in patients with CML who have had splenic irradiation due to significant technical surgical difficulty from the radiation-induced scarring and fibrosis.

Bleeding and infection are the greatest perioperative risks after splenectomy for hypersplenism. Qualitative platelet function should be evaluated rather than relying on a platelet count. The template bleeding time is currently the most widely available laboratory value for identifying adequacy of platelet function. The patient's current and recent medications should be carefully reviewed to identify any drugs that may impair coagulation.

Although splenectomy may be performed through either a midline or a subcostal approach, the midline incision is preferred when coagulation defects, thrombocytopenia, or splenomegaly is present. After the splenic pedicle is clamped, thrombocytopenic patients are transfused with fresh platelets. Careful hemostasis at the conclusion of the procedure is mandatory. Postoperatively, patients should be monitored closely during the first 48 hours for signs of bleeding. A blood cell count with differential and platelet counts should be obtained every 6 hours for the first 24 hours after the operation. Decreasing platelet and blood counts, despite adequate replacement, suggest an ongoing bleeding process.

Open Splenectomy for the Massively Enlarged Spleen

Indications for splenectomy in patients with massively enlarged spleens include debilitating symptoms of splenomegaly, excessive destruction of blood components, and concerns of possible splenic rupture. These patients often complain of chronic severe upper abdominal and back pain, impaired respiration, and early satiety. Hypersplenism may be present. Depending on the size of the spleen and the body habitus, the patient may be judged to be at increased risk of splenic trauma.

Preoperatively, it is important to check quantitative and qualitative platelet function values and coagulation studies because hemorrhage is the major complication of splenectomy in this group. Portal venous contrast studies should be performed in patients with possible portal hypertension.

Adequate blood products must be available preoperatively. The blood of

these patients may be difficult to crossmatch because of numerous past transfusions, and fresh single-donor platelets may be required. Patients should undergo routine bowel preparation, and prophylactic antibiotics should be given.

A midline, rather than subcostal, incision is preferred because the rectus muscles are not severed, which limits bleeding. With increasing size, the spleen becomes more of a midline structure and lends itself to this approach. Before mobilization of the spleen, its vessels should be isolated. The gastrocolic omentum is divided, the lesser sac is entered, and the splenic artery is identified along the posterior–superior surface of the pancreas. The artery is ligated but left intact. The splenic vein is not disturbed yet. The spleen may decrease 20% to 30% in size at this point and allow platelet transfusion without consumption. The splenic flexure of the colon is mobilized, the splenic ligaments are divided, and the spleen is delivered from the splenic fossa. The normally avascular splenic ligaments often contain small vessels in the presence of hematologic malignancies. Dense adhesions between the spleen and the diaphragm may complicate mobilization, and when dissection is particularly difficult, it is better to resect part of the diaphragm with the spleen than to risk hypertrophy of splenic remnants. Such adhesions are formed in areas of splenic infarction and are the most frequent sites of postoperative bleeding in this group of patients.

After the spleen is mobilized, the artery and vein are suture ligated and divided. Liver biopsy may be indicated if involvement by lymphoma is suspected. If an injury to the pancreatic tail is recognized, it should be repaired and drained appropriately. Achieving hemostasis in the splenic bed is crucial and may require suture ligation, cautery, platelet transfusions, and thrombostatic agents. Drains are not routinely used, except in cases of pancreatic injury. Postoperatively, patients should be closely monitored for signs of bleeding or infection.

Laparoscopic Splenectomy

The laparoscopic approach has several advantages over open splenectomy, most obviously, less morbidity from smaller incisions. Other advantages include shorter length of stay, less pain and need for narcotics, and fewer complications. Overall, a laparoscopic approach has also been associated with lower mortality as compared with open surgery. For benign hematologic disease and splenic tumors, laparoscopic splenectomy has

become the standard approach. For malignant conditions without contraindications, its role has been generally accepted provided that fundamental oncologic surgical principles are observed.

Absolute contraindications for a laparoscopic approach include emergent conditions such as splenic rupture. Relative contraindications to laparoscopic splenectomy include uncorrected coagulopathy, severe portal hypertension, and pregnancy; however, there have been successful reports in all of these conditions.

A lateral approach, anterior approach or hand-assisted technique can be used. With the lateral approach, the patient is positioned in the right lateral decubitus position. It is important to prepare a wide field as conversion to open surgery may be necessary. Pneumoperitoneum is established using either an open cut down technique or with the use of an optical trochar after insufflation with a Veress needle. Of note, use of the Veress needle is contraindicated in patients with massive splenomegaly and children (due to limited working domain). A total of 4 trochars are placed; the first in the mid-clavicular line, 2 to 6 cm below the costal margin. The remaining 3 ports are placed 3 to 4 cm below the inferior tip of the spleen; one placed in the subxiphoid region (under the left costal margin), another at the anterior axillary line below the left costal edge. The final trochar is usually placed laterally, off the tip of the 11th rib once the splenic flexure has been mobilized. Trochar sizes can range from 5 to 12 mm, as per the surgeon's preference. Surgery proceeds with a diagnostic laparoscopy to identify accessory spleens, which are present in 12% to 32% of patients. The splenic attachments are then divided in the following order: the splenocolic ligament, splenorenal ligament (inferior pole vessels), gastrosplenic ligament (short gastric vessels), and the splenophrenic ligament. The order can vary however, according to surgeon preference. An energy device (e.g., ultrasonic coagulation shears or bipolar sealing device) can facilitate hemostasis when dividing these attachments. Once the spleen has been mobilized, it is elevated to expose the hilum. Care must be taken to avoid the tail of the pancreas when ligating the splenic vasculature with an endoscopic stapler. The spleen can then be placed into a retrieval sac and partially exteriorized via the 12-mm port site where morcellation can ensue. In some instances, extraction of an intact spleen is necessary for pathologic diagnosis. Drains are not necessary unless injury to the pancreatic tail is a concern.

The anterior approach is seldom used except in instances where the

spleen is very large or if use of a hand-assisted device is anticipated. With the patient in lithotomy position, the surgeon stands between the patient's legs. Access to abdominal cavity is obtained at the umbilicus, usually with an open cut down approach. Trochars are again placed in a fashion similar to the semicircle in the left upper quadrant described above. The liver and stomach are retracted medially. The splenocolic attachments are released and the lower pole of the spleen is elevated to expose the splenic hilum. The splenic artery is then ligated using clips. Use of a stapling device is discouraged since it can be difficult to identify the plane between the tail of the pancreas and the splenic hilum with the anterior approach. The gastrosplenic ligament is then released and remaining splenic attachments dissected. The spleen can then be removed via a retrieval sac.

The hand-assisted laparoscopic surgery (HALS) approach is often used as a bridge between open and laparoscopic splenectomy. This hybrid approach may also be helpful in manipulating a larger spleen. In particular, it can be especially helpful when spleens are >20 cm in size. A hand-port can be used with either a lateral or anterior approach. The nondominant hand is placed into the abdomen via an incision that is generally 7 to 8 cm long and located 2 to 4 cm caudal to the inferior pole of the spleen. A hand-assisted device is then inserted and allows for medial retraction of the spleen. The remainder of the procedure proceeds as described above.

Complications of laparoscopic splenectomy are similar to those with open surgery and include bleeding, pancreatic tail injury, portal vein thrombosis, and overwhelming postsplenectomy infection (OPSI). Postoperative bleeding occurs in approximately 3% of laparoscopic cases. Portal vein thrombosis can occur in 0.7% to 14% of patients and is more common in patients with splenomegaly, myeloproliferative disorders, and hemolysis.

Prophylaxis for Asplenic Sepsis

Patients with hematologic malignancies who undergo splenectomy are at greater risk for asplenic sepsis than are those who have the procedure for other indications (i.e., trauma). Some patients with hematologic malignancy, especially those with CML and CLL, are at increased risk for sepsis even before splenectomy. The risk of OPSI is greatest for children. The expected death rate from OPSI in children is 1 in every 300 to 350 patient-years, and in adults, 1 in every 800 to 1,000 patient-years. For all patients, the risk is greatest for the first few years following splenectomy,

but deaths attributed to OPSI have occurred 30 or more years after splenectomy. *Streptococcus pneumoniae* is the most common infecting organism.

Following splenectomy, there is loss of the opsonins, tuftsin, and properdin, a decrease in immunoglobulin M production, impaired phagocytosis, and altered cellular immunity. Poorly opsonized bacteria are best cleared by the spleen, and following the spleen's removal, patients are particularly susceptible to encapsulated bacteria.

Vaccination can decrease the risk of postsplenectomy pneumococcal infection. The 23-valent form of the pneumococcal vaccine should be used. The vaccine is most effective when given several weeks preoperatively. Nevertheless, despite the diminished immunity obtained if the vaccine is given after splenectomy, adequate protection is still achieved in most patients if administered after 2 weeks postoperatively. Booster immunizations with the pneumococcal vaccine have no proven benefit, although reimmunization at 3 to 5 years may be required if a decrease in specific antibody levels is documented. Certain subsets of patients are at increased risk of infection with *Haemophilus influenzae* and *Neisseria meningitidis* and, therefore, patients should receive these vaccinations as well. Patients are also instructed to keep a supply of antibiotics such as amoxicillin or Augmentin (amoxicillin/clavulanate potassium) with them, which should be taken at the first sign of a febrile episode. This should also be followed by immediate contact with a physician.

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19 Genitourinary Cancer

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INTRODUCTION

Global cancer statistics reveals that genitourinary cancers represented approximately 13.7% of new cancers diagnosed worldwide in 2012. These cancers occur in approximately 300,000 patients within the United States each year. Recognizing these facts, practicing physicians require an essential understanding of the diagnosis and treatment of these diseases. In this chapter, we review the current management of prostate, bladder, renal, and testicular neoplasms.

PROSTATE CANCER

Epidemiology and Etiology

In men, prostate cancer is the most common malignancy and the second leading cause of solid tumor mortality. In the United States, it is estimated that one of seven men will be diagnosed with prostate cancer during their lifetime. Prostate cancer alone accounted for 21% of estimated new cancer cases in 2016. Nearly 2.8% (1 in 39) of men will die from their disease. Prostate cancer screening was introduced in the United States in 1986. Since this introduction, the pattern of disease incidence has changed. From 1988 to 1992, the annual percent increase of prostate cancer incidence was estimated at 17.5% per year. From 1992 to 1995, the incidence decreased to 10.3% per year. This decrease has leveled off and from 1995 to 1997, the average annual decrease in incidence was 2.1%, and the average annual incidence was 149.7 cases per 100,000. These cancer trends are not equivalent between whites and African Americans. Prostate cancer incidence in white males is 123 per 100,000 compared to 208.7 per 100,000 in African Americans, while the resulting mortality is 19.9 per 100,000 versus 47.2 per 100,000, respectively (2008 to 2012). Furthermore, although the average annual mortality rates have decreased

3.6% per year (2003 to 2012) overall, African Americans have experienced a similar decrease in the average mortality rate compared to white males (3.6% vs. 3.4%), respectively per year, between 2003 and 2012. African Americans used to have 2.4-fold higher mortality rate than white males. It is unclear whether the increased mortality rate of prostate cancer in African Americans is due to unique racial biologic and genetic factors, rather than dietary influences, the existence of confounding medical comorbid conditions, lifestyle differences, and/or access to health care issues. Occupational exposure to cadmium has been associated with increased risk of prostate cancer, but this relationship is not yet proven to be causal.

Over 60% of new cases are diagnosed in men aged 60 years and older, and the mean age at diagnosis is 67 years. Prostate cancer rarely occurs before the age of 50 years, and the incidence increases through the ninth decade of life; however, some of this increase may be attributable to an increase in prostate cancer screening in the later decades. It is estimated that 30% to 50% of men older than 50 years have histologic evidence of prostate cancer at autopsy, while at the age of 75 or older, it is estimated that this figure increases to 50% to 70%.

Many factors have been proposed to be associated with the development of prostate cancer. The presence of an intact hypothalamic–pituitary–gonadal axis and advanced age are the most universally accepted risk factors. Migration studies support a role for environmental influences on prostate cancer. Higher rates of prostate cancer have been found among populations with higher amounts of fat in the diet. Beneficial dietary associations include isoflavonoids and lycopenes. Until recently, selenium and vitamin E were considered to exert a protective effect against prostate cancer. However, the Selenium and Vitamin E Cancer Prevention Trial (SELECT trial, 2009) showed no difference in prostate cancer incidence in subjects who received selenium and vitamin E. Two large prospective trials have shown that inhibiting 5-alpha reductase (which converts testosterone into dihydrotestosterone [DHT]) can prevent prostate cancer in a subset of patients. The Prostate Cancer Prevention Trial (PCPT trial, 2003) reported a 24.8% decrease in the incidence of prostate cancer in patients on finasteride when followed for 7 years; however, high-grade cancer rates was increased, which was later reported as an artifact resulting from shrinkage of the prostate and selective inhibition of low-grade cancers. The Reduction by Dutasteride of Prostate Cancer Events

(REDUCE, 2010) reported that dutasteride also decreased prostate cancer incidence by 22.8% over 4 years, but with no associated increase in high-grade cancers.

Evidence has shown that a man with 1, 2, or 3 first-degree relatives affected with prostate cancer has a 2, 5, or 11 times greater risk, respectively, of the development of prostate cancer than the general population. A Mendelian pattern of autosomal dominant transmission of prostate cancer accounts for 43% of disease occurring before the age of 55 years and 9% of all prostate cancers occurring by the age of 85 years. Recent data have implicated the 8q24 chromosomal locus as a risk factor for prostate cancer.

Anatomy

The normal prostate gland weighs 15 to 20 g and is divided into three major glandular zones. The *peripheral zone* constitutes 70% of the prostate gland and is the area palpated during digital rectal examination (DRE). The area around the ejaculatory ducts is called the *central zone* and accounts for 25% of the gland. The *transitional zone* comprises 5% of the prostate gland around the urethra. In a pathologic review of 104 prostate glands from patients who underwent radical prostatectomy, 68% of the cancers were located in the peripheral zone, 24% in the transitional zone, and only 8% in the central zone. Almost all stage T1 (nonpalpable) cancers in that study were found in the transitional zone, the area most susceptible to benign prostatic hyperplasia, which can be associated with urinary symptoms secondary to bladder neck obstruction.

Screening

Although good screening methods for prostate cancer are available, controversy surrounds the concept of screening for this disease. It is estimated that less than 10% of men with prostate cancer die because of the disease. This leads to a lack of consensus on the optimal management of early-stage disease and to questions regarding the cost-effectiveness of a national screening effort for all men older than 50 years. Two large randomized studies recently questioned the utility of screening for prostate cancer. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO, 2009) compared one group of men that underwent prostate-specific antigen (PSA) screening with another group that did not undergo

screening, and found no difference in mortality rates from prostate cancer. However, almost 44% of the patients in both arms of this trial underwent PSA testing prior to enrollment in the trial. On the other hand, the European Randomized Study of Screening for Prostate Cancer (ERSPC, 2009) reported that screening with PSA resulted in a 21% reduction in the rate of death from prostate cancer, but was associated with a high risk of overdiagnosis. As such, in 2012 the US Preventive Services Task Force recommended against PSA screening on the grounds that there is no net benefit and that the potential harms outweigh the benefits. Currently, the American Urological Association (AUA) recommends against routine screening in men between ages 40 and 54 years at average risk of prostate cancer. AUA recommends shared decision-making for men aged 55 to 69 years with a life expectancy of at least 10 years who are considering PSA screening, and proceeding based on patients' values and preferences. Routine PSA screening is not recommended in men over age 70 or any man with less than 10 to 15 years life expectancy. The American Cancer Society recommends discussing screening with patients and offering a DRE and measurement of PSA starting at the age of 50 years for men with a life expectancy of at least 10 years. Screening should begin at age 45 for African-American men or men with one first-degree relative with prostate cancer, and at age 40 for men with even higher risk, such as history of prostate cancer in many first-degree relatives, diagnosed at an early age.

Diagnosis

Patients with low-volume, clinically localized prostate cancer are typically asymptomatic; abnormalities are detected by DRE, increased serum PSA level, or both. Advanced prostate cancer can be asymptomatic; present as local symptoms of urinary hesitancy, frequency, and urgency; or present as systemic symptoms of weight loss, fatigue, and bone pain. Rarely, neurologic sequelae of impending spinal cord compression secondary to bone metastasis or uremia secondary to bilateral ureteral or bladder neck obstruction can be found in the presentation of advanced cases.

PSA is a serine protease produced by the epithelium of the prostate. PSA is not specific for prostate cancer and can be increased in benign conditions of the prostate such as prostatitis, prostatic infarction, and benign prostatic hyperplasia. Traditionally, a PSA threshold of 4 ng/mL was used as a trigger to perform a biopsy. This PSA threshold has been lowered recently to 2.5 ng/mL, although the risk of cancer is also

dependent on age, prostate volume, and PSA velocity. In fact, prostate cancer can be found in 6.6% of men with PSA <0.5 ng/mL, 10.1% of men with PSA 0.6 to 1.0 ng/mL, 17% of men with PSA 1.1 to 2.0 ng/mL, 23.9% of men with PSA 2.1 to 3.0 ng/mL, and 26.9% of men with PSA 3.1 to 4.0 ng/mL. It can also be increased as a consequence of recent ejaculation, and patients should be counseled to abstain from sexual activity for periods of up to 1 week prior to PSA screening. Transurethral resection of the prostate (TURP) and prostatic needle biopsy significantly increase the serum PSA level above baseline for up to 8 weeks. DRE (without prostate massage), cystoscopy, and transrectal ultrasound (TRUS) do not alter serum PSA to a clinically significant degree. The positive predictive value of a PSA level greater than 4 ng/mL for the detection of prostate cancer is 34.4%, while the positive predictive value for an abnormal DRE is 21.4%. Detection rates demonstrate that DRE and PSA together (5.8%) are superior to either DRE (3.2%) or PSA (4.6%) alone. Free PSA is a form of PSA not conjugated to protease inhibitors in the serum. Decreased percentage-free PSA (<25%) is associated with prostate cancer, and measurement of free PSA is performed to improve the specificity of PSA testing in the range of 4 to 10 ng/mL and thus eliminate unnecessary biopsies. The primary utility of free PSA is in the patients with a PSA in the 4 to 10 ng/mL range with a history of previously negative prostatic biopsies. In this clinical scenario, the free to total PSA ratio, or alternatively, complexed PSA, can be used to determine the need for repeat biopsies with continued elevation of the serum PSA. A low free to total PSA ratio (<20%) is an indication to repeat a TRUS biopsy of the prostate to rule out the presence of carcinoma.

TRUS is performed using real-time imaging with a 7-MHz transducer, which allows both transverse and sagittal imaging of the prostate gland. Prostate cancer can appear as a hypoechoic region within the prostate, although most experts agree that this is a nonspecific finding. TRUS can also be used to measure the dimensions of the prostate gland to calculate the glandular volume.

Pelvic lymphatic metastases can be detected by computed tomography (CT) or magnetic resonance imaging (MRI). The risk of pelvic nodal metastasis depends on tumor grade, clinical stage, and PSA level. Nomograms incorporating these three factors have been developed to predict the risk of nodal metastasis. However, the only definitive method for staging pelvic lymph nodes is a pelvic lymphadenectomy.

Radionuclide bone scan remains the most sensitive test to detect skeletal metastases. However, in 1993, Oesterling found the yield of a bone scan was 2% if a patient has a PSA level less than 20 ng/mL and evidence of skeletal metastasis, while no patients had a positive bone scan with a PSA less than 8 ng/mL. Therefore, based on this data, radionuclide bone scans are not necessary for staging prostate cancer in patients who have a low serum PSA level (<10 ng/mL) and no skeletal symptoms, particularly in cases of low-grade cancers. When bone metastases are present, 80% are osteoblastic, 15% are mixed osteoblastic–osteolytic, and 5% are osteolytic. A chest radiograph is performed to detect the presence of pulmonary metastases, which are extremely rare.

The diagnosis of prostate cancer is made by the histologic finding of prostate cancer in a prostatic biopsy, in tissue obtained from prostatectomy for benign disease, or in the biopsy of a suspicious metastatic focus. In the past, sextant biopsies of the prostate were considered adequate in the patient with an elevated PSA, with site-specific biopsies directed at palpable or ultrasonographic abnormalities (hypoechoic regions). More recent data based on whole mount step sectioning of radical prostatectomy specimens suggest that sextant biopsies are inadequate, in favor of 12 core strategies that focus on the peripheral zone, but also include the anterior horns of the prostate and the transition zone bilaterally. Adenocarcinoma is the predominant cell type of prostate cancer and is the only type discussed in this chapter.

Grading and Staging

The Gleason grading system is the most widely used grading system. It recognizes five histologic patterns of prostate cancer, graded on a scale of 1 to 5, from most to least differentiated. The Gleason score is arrived at through the addition of the predominant and secondary grade patterns to yield a range of tumor Gleason scores from 2 to 10, with most prostate cancers falling in the Gleason 5 to 10 range. Prostate cancer is well known to be multifocal in nature, so not uncommonly, multiple biopsies from a prostate may be positive, each with a reported Gleason score. The biology of the cancer is frequently dictated by the most aggressive variant found in the prostate.

The biologic behavior of the tumor can be further categorized by stage, which accounts for tumor volume and location. Prostate cancer typically spreads to the pelvic lymph nodes, bone, and lungs. Prostate cancer staging

of the 2010 American Joint Committee on Cancer is shown in Table 19.1.

Once a diagnosis of prostate cancer is made, risk assessment becomes paramount in guiding treatment decisions and for counseling patients accurately about expected oncologic and functional outcomes. The AUA and the National Comprehensive Cancer Network (NCCN) both have similar risk stratification systems that are primarily based on PSA level, Gleason score, and clinical stage. Prostate cancer risk stratification is shown in Table 19.2.

Management of Early Disease

In 1987, the National Cancer Institute published a consensus statement on the treatment of early-stage prostate cancer. The report concluded: "Radical prostatectomy and radiation therapy are clearly effective forms of treatment in the attempt to cure tumors limited to the prostate for appropriately selected patients…. What remains unclear is the relative merit of each in producing lifelong freedom from cancer recurrence…. Properly designed and completed randomized trials that evaluate both disease control and quality of life after modern radiation therapy compared with radical prostatectomy are essential." These criteria have yet to be fulfilled and probably never will; however, there appears to be little difference in clinical and biochemical outcomes between the two modalities when similar patient groups are compared.

TABLE 19.1 Staging Systems for Prostate Cancer

Primary Tumor Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
	T1a: Tumor incidental histologic finding in 5% or less of tissue resected
	T1b: Tumor incidental histologic finding in more than 5% of tissue resected
	T1c: Tumor identified by needle biopsy because of increased PSA
T2	Tumor confined within the prostate gland
	T2a: Tumor involves one-half of one lobe or less
	T2b: Tumor involves more than one-half of one lobe, but not both lobes
	T2c: Tumor involves both lobes
T3	Tumor extends through the prostate capsule
	T3a: Extracapsular extension (unilateral or bilateral)
	T3b: Seminal vesicle invasion
T4	Tumor is fixed or invades the bladder, rectum, external sphincter, levator muscles, or pelvic side wall

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes

Distant Metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
	M1a: Nonregional lymph nodes
	M1b: Bone(s)
	M1c: Other site(s) with or without bone disease

Prostate Cancer—Anatomic Stage/Prognostic Groups

Group	T	N	M	PSA	Gleason
I	T1a–T2a	N0	M0	<10	≤6
	T2a	N0	M0	<10	≤6
	T1a–T2a	N0	M0	X	X
IIA	T1a–c	N0	M0	<20	7
	T1a–c	N0	M0	≥10 <20	≤6
	T2a	N0	M0	<20	≤7
	T2b	N0	M0	<20	≤7
	T2b	N0	M0	X	X
IIB	T2c	N0	M0	Any	Any
	T1–T2	N0	M0	≥20	Any
	T1–T2	N0	M0	Any	≥8
III	T3a–T3b	N0	M0	Any	Any
IV	T4	N0	M0	Any	Any
	Any T	N1	M0	Any	Any
	Any T	Any N	M1	Any	Any

PSA, prostate-specific antigen.

TABLE **19.2** Prostate Cancer Risk Stratification

Category Level	AUA Risk Category	NCCN Risk Category
Very low	N/A	PSA ≤10 ng/mL, Gleason score ≤6, clinical stageT1c, <3 positive biopsy cores, ≤50% in each core, and PSA density <0.15 ng/mL/g
Low	PSA ≤ 10 ng/mL, Gleason score ≤6, clinical stage T1c or T2a	PSA <10 ng/mL, Gleason score ≤6, clinical stage T1 or T2a
Intermediate	PSA >10–20 ng/mL, Gleason score >7, or clinical stage T2b	PSA 10–20 ng/mL, Gleason score 7, or clinical stage T2b–T2c
High	PSA >20 ng/mL, Gleason score 8–10, or clinical stage ≥T2c	PSA >20 ng/mL, Gleason score 8–10, or clinical stage T3a
Very high	N/A	Primary Gleason pattern 5 or >4 cores with Gleason score 8–10, or clinical stage T3b–T4

Active Surveillance

Active surveillance (AS) is defined as a treatment strategy in which men with low-risk prostate cancer are serially monitored for disease

progression and then treated definitively (if needed), thereby avoiding or delaying the risk of treatment-related morbidity. Importantly, AS differs from observation/watchful waiting (WW) as the latter indicates a decision to avoid/forgo definitive therapy and palliate only if there is metastatic progression. Entry criteria for AS protocols vary from institution to institution. Typically, men with very low-risk and low-risk prostate cancer per AUA and NCCN guidelines (Table 19.2) or clinically insignificant disease per Epstein criteria are candidates for AS. An initial repeat biopsy and/or multiparametric prostate MRI may aid in reclassifying men with higher-risk disease.

In 2005, Bill-Axelson et al. prospectively compared surveillance with radical prostatectomy in patients with PSA <50 and clinical stage T2 or less, and found that patients who underwent radical prostatectomy were less likely to develop metastases (15% vs. 25%) and less likely to die of prostate cancer (10% vs. 15%). This reduction in prostate cancer deaths was most significant in patients younger than 65 years of age. Klotz et al. recently reported on 450 patients with low-risk prostate cancer that underwent AS. During follow-up, 30% of patients were classified as high risk and 117 underwent radical therapy, of whom 50% experienced treatment failure. Patients with a fast PSA doubling time (less than 3 years) were at a higher risk of treatment failure. Overall survival was 78%, while 10-year actuarial prostate cancer–specific survival was 97%, indicating that most deaths resulted from causes other than prostate cancer. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) found that radical prostatectomy did not improve overall or disease-specific mortality. Radical prostatectomy was associated with reduced all-cause mortality among men with a PSA value greater than 10 ng/mL ($p = 0.04$ for interaction) and possibly among those with intermediate-risk or high-risk tumors ($p = 0.07$ for interaction). The median 10-year follow-up and less than average health of men in the PIVOT study suggest only men with competing risks may safely be offered AS.

Cryotherapy

Prostate cryotherapy has been used since 1996. The current third-generation cryotherapy uses high-quality TRUS guidance, an argon-based freezing system, multisensor temperature probes, and a urethral warming device. These features give urologists excellent control of ice ball formation during cryotherapy. Cryotherapy is typically reserved for early-

stage, low-volume and low-grade disease. Large contemporary series have shown a 5-year disease-free survival rate of 77% for primary cryotherapy. The incidence of reported complications in the literature after primary cryotherapy for erectile dysfunction, urinary incontinence and fistula formation range between 49% and 93%, 1% and 8%, 0% and 0.5%, respectively. Focal cryotherapy has been investigated as an alternative, but is not widely accepted at present. The main use of cryotherapy though is in patients who have local prostate recurrence after radiation therapy (so-called salvage cryotherapy for radiorecurrent prostate cancer). In this patient population, the 5-year disease-free survival rate decreases to 58.9%.

Surgery

The surgical excision of prostate cancer by complete removal of the prostate gland, seminal vesicles, and ampullae of the vasa deferentia was first performed in the early 1900s. This procedure, known as a *radical prostatectomy*, can be performed using a perineal or retropubic approach. In the last decade, minimally invasive surgical techniques such as laparoscopic radical prostatectomy and robot-assisted laparoscopic prostatectomy have become mainstream, with similar oncologic and functional outcomes (continence and erectile function), but less blood loss, narcotic and transfusion requirements, and shorter hospital stays compared to open techniques. In 2010, it was estimated that 67% to 85% of all prostatectomies performed in the United States were done using robot-assisted techniques. Zincke et al. reported their experience with radical prostatectomy in 1,143 patients with 10- and 15-year cause-specific survival rates of 90% and 83% and metastasis-free survival of 83% and 77%, respectively. Complication rates are low. Mortality is less than 0.7% and the incidence of severe incontinence is 1.4%. In 1992, Leandri et al. reported on 620 patients and found a 6.9% early complication rate, 1.3% late complication rate, and 0.2% mortality rate. Sexual potency was maintained in 71% in whom a nerve-sparing technique was used, and 5% experienced stress incontinence after 1 year. Factors that predict for postoperative potency include preoperative erectile function, patient age, and number of cavernosal nerve fibers spared. Factors that influence continence results include nerve sparing, patient age, and obesity. Bilateral pelvic lymph node dissection (PLND) is considered an essential part of radical prostatectomy, especially for high-risk disease. It provides accurate

staging, prognostication, and may have a therapeutic benefit. A standard PLND includes removal of lymphatic tissue around the external iliac vein down to the internal iliac artery as well as tissue within the obturator fossa. Proximally, dissection continues up to the bifurcation of the common iliac artery, and distally to Cooper's ligament.

Radiation Therapy

Brachytherapy and external-beam radiation therapy (EBRT) are used for the definitive treatment of localized prostatic adenocarcinoma. Permanent brachytherapy typically uses Palladium-103 (doses of 125 Gy) or Iodine-125 (doses of 145 Gy) and is mainly reserved for patients with small prostates and low-risk prostate cancer (PSA <10, Gleason 6 or less, and clinical stage T2a or less). For patients with intermediate or high-risk prostate cancer, brachytherapy should not be given as single-modality therapy, and needs to be combined with EBRT. Intensity-modulated radiation therapy (IMRT) is currently used to decrease adverse local side effects of radiation therapy and increase total dosage to the prostate, and is the external-beam radiotherapeutic modality of choice due to improved prostate targeting and side-effect profile compared to previous generation radiotherapy. For low-risk patients, IMRT is used alone at doses of up to 75 Gy, while for patients with intermediate- or high-risk disease, doses up to 80 Gy are given, and are combined with androgen deprivation therapy. At the MD Anderson Cancer Center, we recommend radical prostatectomy for the treatment of prostate cancer in the patient with minimal comorbidities, less than 70 years of age. Primary radiation therapy is reserved for patients with significant comorbid medical illnesses or patients older than 70 years of age. Proton beam therapy (PBT) has emerged with potential superiority in sparing organs at risk such as bladder, rectum, and femoral head when compared with photons. PBT is a specific type of EBRT in which a heavy particle (protons) is used instead of photons. While PBT uses image-guided radiation therapy (IGRT), it uses less lateral fields (1 to 2) rather than (5 to 7) fields required for IMRT. The dosimetric advantage of PBT is that it allows a high dose to be delivered to the prostate similar to IMRT, with less pelvic tissue receiving low to moderate dose. However, the available albeit, limited evidence suggests that the use of PBT in treating prostate cancer offers no confirmed advantage over conventional IMRT.

Management of Locally Advanced Prostate Cancer/Lymph Node Metastasis

Locally advanced prostate cancer involves areas outside the prostatic capsule, such as fat, seminal vesicles, levator muscles, or other adjacent structures. Locally advanced prostate cancer is associated with a 53% incidence of lymph node metastases and decreased overall survival rate compared with early-stage disease. Locally advanced disease with or without lymph node metastasis can be treated with primary radiation therapy and androgen ablation with a 6-year biochemical failure rate of 13%, but longer follow-up is still needed. These patients with locally advanced disease at high risk for relapse are frequently enrolled in clinical protocols that use neoadjuvant systemic therapy in combination with surgical extirpation of the prostate followed by adjuvant radiotherapy to improve patient outcome. Our experience at the MD Anderson Cancer Center with locally advanced disease treated with primary radiation therapy demonstrated 5-, 10-, and 15-year uncorrected actuarial survival rates of 72%, 47%, and 17%, respectively. The local control rate was 75% at 15 years of follow-up.

Treatment modalities other than radiation therapy used for locally advanced disease include radical prostatectomy, TURP, and hormonal therapy. However, currently there is paradigm interest in prostatectomy as part of a multidisciplinary approach to provide local control in selected patients with high-risk locally advanced/node positive disease. Tumor grade, stage, bulk of tumor, and seminal vesicle involvement in locally advanced disease are associated with a decreased interval between radical prostatectomy and disease progression. The actuarial 5-year survival rate for patients with locally advanced disease who have undergone TURP is 64%, making TURP an option for patients with short life expectancies who have significant local symptoms associated with their prostate cancer such as urinary obstruction or intractable hematuria. This strategy may be ideal in the elderly and in those with serious coexisting medical problems.

Metastatic Prostate Cancer

Patients with metastatic prostate cancer have a median survival duration of 30 months, with an estimated 5-year survival rate of 20%. The first-line treatment of metastatic prostate cancer is androgen ablation therapy. The hypothalamus produces luteinizing hormone-releasing hormone (LHRH)

and corticotropin-releasing factor, which stimulate the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH). LH stimulates testosterone production by the testes, and ACTH stimulates the adrenal glands to produce androstenedione and dehydroepiandrosterone, precursors of testosterone and DHT. Although the testes are the major source of testosterone, the adrenal glands can supply up to 20% of the DHT found in the prostate gland.

Androgen ablation therapy consists of either bilateral orchiectomy or LHRH agonists, which chronically stimulate the pituitary gland, resulting in a decrease in LH release. Direct LHRH antagonists are now also available, but they have not gained widespread acceptance over the agonists that have a more extensive clinical background. Decrease in LH leads to castrate levels of testosterone production by the testes, defined typically as less than 50 ng/mL. Several oral antiandrogens exist that work by blocking uptake or binding of androgen in target tissues. Combination of antiandrogens with either surgical or medical androgen ablation is termed combined androgen blockade.

Bilateral orchiectomy and LHRH agonists appear to have equal efficacy when used as monotherapy for metastatic prostate cancer. The Medical Research Council of the United Kingdom performed a randomized prospective trial with 934 patients and found that immediate androgen ablation delays disease progression and decreases pathologic fractures. We recommend immediate androgen ablation for select patients. Combined androgen blockade with an LHRH agonist plus an antiandrogen is controversial. Many studies have shown no benefit to combined therapy with an antiandrogen versus LHRH agonist monotherapy. Intermittent androgen therapy has been demonstrated to improve quality of life, but its long-term effects on survival are unknown. Androgen ablation, although useful as first-line therapy in patients with metastatic prostate cancer, has been shown to increase the risk of osteoporosis, metabolic syndrome and cardiovascular disease. The median survival of patients with hormone refractory disease known as castration-resistant prostate cancer (CRPC) is on the order of 12 to 18 months. The median time to castration-resistant state for patients with metastatic prostate cancer treated with hormonal therapy is approximately 2 years. Chemotherapeutic regimens are the mainstay of therapy for metastatic castration-resistant prostate cancer (mCRPC) with taxane-based regimens showing significant activity that includes decreases in PSA, improved quality of life, objective disease

regression, and prolonged survival. Docetaxel as a potent inhibitor of microtubule assembly and disassembly showed improved survival in the every 3-week regimen of docetaxel plus prednisone (18.9 months vs. 16.5 months in the mitoxantrone group, HR 0.75; $p = 0.009$). Cabazitaxel is another tubulin-binding taxane which showed improved overall survival (15.1 months vs. 12.7 months for mitoxantrone group) in patients who had received prior docetaxel. However, targeted therapy has emerged as an important option in mCRPC. Abiraterone acetate is a steroidal antiandrogen that inhibits CYP17A1 to reduce testosterone production. Prior to docetaxel chemotherapy, 1,088 participants who were randomized to receive 1,000 mg/day of abiraterone plus prednisone 5mg twice daily had statistically significant improvement in radiographic progression-free survival (16.5 months vs. 8.3 months for placebo and prednisone 5 mg twice daily; HR 0.53; $p < 0.001$). The final survival analysis of these chemotherapy-naïve 1,088 men revealed a significantly longer overall survival in the abiraterone group than in the placebo group (34.7 months vs. 30.3 months; HR 0.81; $p = 0.0033$). Similarly, a post-docetaxel randomized phase 3 study showed abiraterone significantly prolonged overall survival in patients with mCRPC who have progressed after docetaxel treatment compared to placebo plus prednisone (15.8 months vs. 11.2 months, respectively; HR 0.74; $p < 0{\cdot}0001$). Enzalutamide is another targeted treatment option for men in the pre- and post-docetaxel mCRPC setting and for those who are not candidate for chemotherapy.

Enzalutamide is a competitive inhibitor of androgen binding and also inhibits nuclear translocation of the androgen receptor, DNA binding and coactivator recruitment. The AFFIRM trial randomized 1,199 men with CRPC after chemotherapy to receive enzalutamide 160 mg per day (800 patients) or placebo (399 patients). The study showed that enzalutamide significantly prolonged survival of men with mCRPC (18.4 months vs. 13.6 months in the placebo group; HR 0.63; $p < 0.001$). The AFFIRM trial also confirmed enzalutamide significantly improved time to first skeletal-related event, pain control, and patient-reported health-related quality of life in post-docetaxel patients with mCRPC. In the phase 3 PREVAIL study which involved 1,717 asymptomatic or mildly symptomatic patients and those who had not received prior chemotherapy, ketoconazole, or abiraterone were randomized to receive either enzalutamide at a dose of 160 mg or placebo once daily. Enzalutamide significantly decreased the risk of radiographic progression at 12 months (65% vs. 14% for patients

receiving placebo, 81% risk reduction; HR 0.19; $p < 0.001$). Chemohormonal trials involving the use of docetaxel and ADT in hormone-sensitive metastatic prostate cancer revealed significantly longer overall survival in combination arms in the CHAARTED trial (57.6 months vs. 44.0 months for ADT alone; HR 0.61; $p < 0.001$) and in the STAMPEDE trial (5.4 years vs. 3.6 years for ADT alone, $p = 0.006$).

The autologous cancer vaccine Sipuleucel-T was approved by the FDA for minimally or asymptomatic patients with CRPC. It is an intravenous immunotherapeutic agent shown to decrease overall mortality by 33% compared to placebo. In addition to antineoplastic therapy, patients with metastatic prostate cancer typically receive bone-protecting agents (such as the bisphosphonate zoledronic acid), especially when hormone ablation is instituted. Clinical trials continue to be the main and best treatment option for patients; however, some treatment options (primarily taxane-based chemotherapy regimens) now exist that demonstrate objective benefit where none existed previously.

Radium-223 dichloride, an alpha emitter, selectively targets bone metastases with alpha particles. A randomized phase 3 trial was conducted involving 921 patients with histologically confirmed, progressive CRPC with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases. These patients were not eligible to receive or declined docetaxel, were randomized to receive six injections of radium-223 (at a dose of 50 kBq/kg of body weight intravenously) or matching placebo. Results confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; HR 0.70; 95% CI, 0.58 to 0.83; $p < 0.001$).

BLADDER CANCER

Epidemiology and Etiology

Bladder cancer is the second most common genitourinary malignancy in the United States. It is the fourth most common cancer in men and the tenth most common cancer in women. In 2016, approximately 76,960 new cases were expected, and 16,390 estimated deaths were attributed to bladder cancer. The lifetime probability of developing bladder cancer is 1 in 26 in males and 1 in 88 in females, and is lower for African Americans compared to whites.

The etiology of bladder cancer, of which urothelial (or transitional cell) carcinoma is the most common, is well established. Cigarette smoking has

been linked to 30% to 40% of all cases of bladder cancer. The chemicals 1-naphthylamine, 2-naphthylamine, benzidine, and 4-aminobiphenyl have been shown to promote urothelial carcinogenesis. Workers in the textile, leather, aluminum refining, rubber, and chemical industries who are exposed to high levels of these chemicals have an increased incidence of bladder cancer. Other chemicals that have been linked to urothelial cancer are MBUCCA (plastics industry), phenacetin, and the antineoplastic agent cyclophosphamide. In addition, recurrent bladder infections, as well as infections with the parasite *Schistosoma haematobium*, have been associated with squamous cell carcinoma of the bladder.

Pathology

The urinary bladder is a hollow viscus that functions in both the storage and the evacuation of urine. Histologically, the bladder is composed of mucosa, lamina propria, muscularis propria, and serosa (limited to the dome). Localized bladder cancer is classified as *nonmuscle invasive bladder cancer (NMIBC)*, which is limited to the mucosa and lamina propria, or *muscle invasive disease (MIBC)*, which extends into the muscularis propria and beyond. Approximately 70% of newly diagnosed bladder cancers are NMIBC, whereas the remaining 30% are invasive. Once a bladder cancer extends through the basal layer of the mucosa, it may invade blood vessels and lymphatics, thereby providing a route of metastasis. *Carcinoma in situ (CIS)*, an aggressive form of NMIBC, is composed of flat, high-grade urothelial carcinoma limited to the mucosal layer.

The World Health Organization (WHO) classifies epithelial tumors of the bladder into four histologic types: urothelial carcinoma (91%), squamous cell carcinoma (7%), adenocarcinoma (2%), and other variants of urothelial carcinoma (<1%). However, up to 20% of urothelial carcinomas contain areas of squamous differentiation, and up to 7% contain areas of adenomatous differentiation. The remainder of this section discusses urothelial carcinomas.

Clinical Presentation

Eighty percent of all patients who present with bladder carcinoma have gross or microscopic hematuria, typically painless and intermittent. Approximately 20% of patients complain of irritative voiding symptoms,

including urinary frequency, urgency, dysuria, and stranguria particularly with CIS. Other symptoms include pelvic pain, flank pain (from ureteral obstruction), and lower extremity edema. Patients with systemic disease may present with anemia, weight loss, and bone pain.

Diagnosis

A patient who presents with hematuria or other symptoms of bladder cancer should undergo a thorough urologic evaluation consisting of a history, physical examination, urinalysis, cystoscopic examination of the urinary bladder, voided urine for cytologic examination, and intravenous contrast-enhanced CT scan of the abdomen and pelvis. The most useful of these steps is the direct visual examination of the bladder using a flexible cystoscope in the office. Papillary and sessile tumors are easily visualized through the cystoscope; CIS, however, can appear as normal mucosa or as erythematous patches throughout the bladder. Endoscopic evaluation has traditionally used white-light cystoscopy but more recently blue-light cystoscopy with intravesical instillation of hexaminolevulinate has emerged as an adjunct with an increased detection rate of bladder cancer particularly for CIS. Fewer than 60% of bladder tumors can be seen on a CT scan, but this examination is obtained primarily to identify other abnormalities that may be present in the upper urinary tract (renal pelvis or ureteral tumors, associated hydronephrosis, etc.) in addition to evaluating the primary bladder tumor, presence of local extension into soft tissues, and presence of regional lymphadenopathy. Urine cytology is reported as positive in ~30% of patients with low-grade tumors, and 65% to 100% of patients with high-grade tumors or CIS (see the next section for definition of grades).

Grading and Staging

The WHO grading system, updated in 2004, is based on the cytologic features of the tumor. Low-grade tumors are well differentiated and high-grade tumors are poorly differentiated.

Once a bladder tumor is diagnosed, the urologist must accurately stage the tumor. The initial transurethral resection of the bladder tumor (TURBT), typically done in association with random biopsies of the bladder and prostatic urethra, will determine the histologic depth of invasion of the tumor and the presence or absence of dysplasia or CIS. A

bimanual examination should be performed at the time of resection to determine whether a mass is present and, if so, whether it is fixed or mobile.

Further workup for detecting metastasis consists of a CT scan, liver function tests, a chest radiograph, and a bone scan (if the alkaline phosphatase level is elevated or the patient's symptoms suggest systemic disease). The American Joint Committee on Cancer TNM staging systems are listed in Table 19.3.

TABLE 19.3 Staging Systems for Bladder Cancer

Primary Tumor Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (flat tumor)
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
	T2a: Tumor invades superficial muscularis propria (inner half)
	T2b: Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
	T3a: Microscopically
	T3b: Macroscopically (extravesical mass)
T4	Invasion of any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall
	T4a: Tumor invades prostate stroma, uterus, or vagina
	T4b: Tumor invades pelvic or abdominal wall

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node in the true pelvis
N2	Metastasis in multiple regional lymph nodes in the true pelvis
N3	Metastasis in a common iliac node

Distant Metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Bladder Cancer—Anatomic Stage/Prognostic Groups

Group	T	N	M
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2a	N0	M0
	T2b	N0	M0
III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1–N3	M0
	Any T	Any N	M1

Management

Nonmuscle Invasive Bladder Cancer

Approximately 70% of bladder cancers present as NMIBC (e.g., Ta, T1, or

Tis). An estimated 70% of these cancers are Ta and 20% are T1. Ten percent of all bladder cancers present with Tis or CIS. After the initial treatment of NMIBC, the disease can be cured, can recur with the same stage and grade, or can recur with progression of stage or grade. Risk factors associated with both disease recurrence and progression include a high tumor grade, lamina propria invasion, tumor diameter larger than 3 cm, vascular or lymphatic invasion, multiplicity, and expression of either epidermal growth factor or transforming growth factor-alpha. Mutations in *TP53* may also be associated with a significant risk of disease progression.

Initial treatment of NMIBC focuses on eradication of the existing disease using transurethral resection of bladder tumor (TURBT) and chemical prophylaxis against disease recurrence or progression. TURBT has been the standard treatment for existing stage Ta and T1 tumors and visible stage Tis tumors. Laser fulguration is another therapeutic option that results in fewer bleeding complications. The advantage of transurethral resection over laser fulguration is that it provides tissue for histologic examination. Patients with apparently NMIBC at the time of TURBT should receive a single dose of intravesical mitomycin C within 6 hours of resection, if no bladder perforation is evident. This single dose has been shown to decrease the risk of bladder cancer recurrence by about 40%. Patients who have T1 disease should undergo a repeat TURBT 2 to 6 weeks after the initial TURBT, as these patients have a 30% risk of being upstaged into T2 disease or higher.

Patients with NMIBC with high risk of recurrence and progression including those with CIS, high-grade Ta or T1 lesions, multifocal and recurrent tumors and rarely residual disease may be candidates for adjuvant intravesical therapy. Intravesical agents can be used as therapeutic, adjuvant, or prophylactic treatment for bladder cancer. Thiotepa, mitomycin C, gemcitabine, and valrubicin are the chemotherapeutic agents used most frequently. Bacillus Calmette—Guérin (BCG), a live attenuated tuberculosis organism, has become the most widely used intravesical agent in NMIBC, typically alone, and less frequently in combination with alpha-interferon. BCG enhances the patient’s own immune response against the tumor, providing resistance to disease recurrence thereby potentially delaying progression. BCG is typically started 4 to 6 weeks after TURBT, as starting BCG too soon after TURBT (before urothelial healing occurs) may result in BCG sepsis. Although specific dose scheduling varies, most treatment regimens include

intravesical treatment weekly for 6 weeks, followed by a series of maintenance treatments administered over 12 to 36 months. BCG has been shown to eliminate CIS in 80% of patients at a 5-year follow-up, reduce tumor recurrence rate for patients with T1 disease to 30% at 4 years, and eliminate residual tumor in up to 59% of patients. Maintenance therapy regimens with BCG appear to offer the best outcomes for patients. In 2000, Lamm et al. randomized 384 patients with NMIBC to receive induction and maintenance BCG or induction BCG therapy alone. Median recurrence-free survival time was longer for those who received induction and maintenance therapy; however, at 5-year follow-up there was no difference in survival. In 2002, Sylvester et al. performed a meta-analysis of 24 clinical trials and found that only patients who received maintenance BCG after TURBT had a decreased risk of progression into muscle invasive disease.

There is good evidence that a T1 high-grade cancer has a high rate of progression and therefore confers a high risk of death. Therefore, we recommend early radical cystectomy (before developing muscle invasion) for select patients with high-grade T1 bladder cancer. Furthermore, we also recommend cystectomy for patients who recur within 1 year despite two induction courses of BCG therapy or BCG maintenance because these patients have been shown to be at high risk for disease progression if their bladder remains in situ.

Invasive Bladder Cancer

Tumors that have penetrated the muscularis propria are considered invasive. Several options are available for treatment of patients with invasive tumors. A small subset of patients may be eligible for bladder-sparing therapy. In 2001, Herr demonstrated a 76% overall survival rate, with 57% of the patients preserving their bladders in 45 patients treated with aggressive transurethral re-resection of invasive bladder tumors (median follow-up: 61 months). Patients with an MIBC that is primary and solitary, does not have associated CIS, usually at the dome of the bladder and allows for a 2-cm surgical margin may be candidates for partial cystectomy. At the MD Anderson Cancer Center, data have shown that approximately 5% of patients are actually suitable for bladder-sparing surgery; 5-year survival rates have been comparable to those achieved with radical cystectomy, when negative margins of resection can be achieved.

Primary EBRT has been used to treat MIBC. Treatment protocols

advocate doses of 65 to 70 Gy. Five-year survival rates range from 21% to 52% for T2 bladder cancer and from 18% to 30% for T3 tumors. Local recurrence occurs in 50% to 70% of these patients. T4 lesions fare worse, with 5-year survival rates consistently less than 10%. Our experience at the MD Anderson Cancer Center found a 26% 5-year survival rate with primary external-beam radiation. Thus, EBRT may be useful in patients who do not want to have surgery or for whom radical surgery is medically contraindicated; however, the results with radiation therapy, stage for stage, are significantly worse than those seen with radical surgery. EBRT alone is also inferior to EBRT with concurrent chemotherapy following TURBT for MIBC.

In an attempt to improve survival and bladder preservation rates, multimodality strategies have combined TURBT, chemotherapy, and radiation. In 1997, Kachnic et al. from Massachusetts General Hospital reported on 106 patients with T2 to T4 bladder cancers who were treated with TURBT, two cycles of methotrexate, cisplatin, vinblastine (MCV), and 40-Gy radiation therapy plus concurrent cisplatin. Overall 5-year survival was 52%, and overall 5-year survival rate with the bladder intact was 43%. These results are comparable to contemporary radical cystectomy series; however, this regimen involves significant morbidity and patient investment in complex treatment schedules. Moreover, patients are subjected to a considerable risk of eventual cystectomy and superficial bladder cancer recurrence.

Radical cystectomy with pelvic lymphadenectomy is performed with the intent of removing all localized and regional lymphatic disease. There is evidence that an extended pelvic lymphadenectomy (starting cranially from the inferior mesenteric artery takeoff) improves detection of nodal metastasis and could have a therapeutic benefit, especially in patients with minimal nodal disease. In 2001, Stein et al. reported on 1,054 patients who were treated with open radical cystectomy and pelvic lymphadenectomy at a single institution. Perioperative mortality was 2.5% and 28% experienced early complications postoperatively. Ten-year recurrence-free survival in node-negative patients was 86% for pT0, 89% for pTcis, 74% for pTa, 78% for pT1, 87% for pT2, 76% for pT3a, 61% for pT3b, and 45% for pT4. Twenty-four percent of all patients had positive lymph nodes, with a corresponding 10-year recurrence-free survival of 34%. Median time to recurrence in this patient cohort was 12 months (22% of patients had distant recurrence, and 7% had a local pelvic recurrence). In

the last decade, several centers have started using laparoscopic and robot-assisted laparoscopic radical cystectomy with extracorporeal or intracorporeal urinary diversion. However, long-term oncologic efficacy for these procedures cannot be evaluated yet due to relatively short follow-up.

Once a patient undergoes cystectomy, the ureters must be diverted into an alternate drainage system. The most common urinary diversions used today are either an ileal conduit (incontinent diversion), or an orthotopic urinary diversion with an ileal segment (continent diversion). Patients who are unable to undergo an orthotopic diversion include patients with elevated serum creatinine, evidence of lymph node metastasis, prostatic urethral invasive urothelial carcinoma or CIS, inflammatory bowel disease or severe urethral stricture disease in male patients. Furthermore, these patients must be willing and able to undergo a vigorous voiding re-education program. Radiation therapy may render continence difficult; therefore, some patients may not benefit from this type of diversion. Catheterizable cutaneous reservoirs such as an Indiana pouch are also used as methods of continent urinary diversion in selected patients. In the end, if a patient is unable to meet these criteria, then a noncontinent diversion with a cutaneous ileal conduit is recommended.

Grossman et al. led a phase 3 randomized trial through SWOG comparing radical cystectomy alone with neoadjuvant chemotherapy followed by radical cystectomy and reported a 5% overall survival benefit with the latter approach. At the MD Anderson Cancer Center, adjuvant chemotherapy is used for select patients with unfavorable disease characteristics, which include resected nodal metastases, extensive extravesical involvement, or involvement of pelvic viscera. Previously, treatment with adjuvant chemotherapy in selected patients at the MD Anderson Cancer Center resulted in a 70% 5-year survival rate, which is comparable to patients without unfavorable features. Currently, several targeted therapies are being investigated in the neoadjuvant and metastatic setting.

Metastatic Disease

Cisplatin appears to be the agent with the greatest activity against urothelial carcinoma of the bladder; however, single-agent therapy response rates are only in the range of 10% to 30%. Traditionally, chemotherapy for bladder cancer included cisplatin, methotrexate,

vinblastine, and doxorubicin (M-VAC). In the MD Anderson Cancer Center trial of M-VAC, a complete response rate of 35% and a partial response rate of 30% were observed. Other trials have documented similar response rates, with a median survival of approximately 1 year. Newer regimens using gemcitabine and cisplatin have demonstrated no significant difference in survival when compared with M-VAC, but adverse side effects and toxicity are decreased with the newer regimen, which is now used most commonly in this setting.

RENAL CANCER

Epidemiology and Etiology

Tumors of the renal and perirenal tissues comprise 3% of cancer incidence and mortality in the United States. Renal cell carcinoma (RCC) represents 85% of all renal parenchymal tumors and is the only renal tumor discussed in this chapter. In 2016, an estimated 62,700 people were estimated to be diagnosed with malignancies of the kidney and renal pelvis, and close to 14,420 people died of this disease. From 1975 to 1995, both the incidence and mortality rates of RCC have increased. The upward trend in mortality rates suggests that the increased incidental diagnosis of early-stage asymptomatic tumors does not fully account for the overall increase in incidence. This rise in incidence is seen more significantly in African Americans. Males are affected twice as often as females. RCC most frequently occurs in the fifth to sixth decades of life.

Several risk factors have been identified to be associated with RCC. Case-control studies have found strong correlations with smoking and obesity. Hypertension, diabetes mellitus, occupational exposure (including cadmium, asbestos, and gasoline) and diuretic use have also been found to be associated with RCC; however, it is unclear whether this is a causal relationship. RCC can occur either sporadically or genetically. Hereditary RCC tends to occur at an earlier age of onset and tends to be bilateral and multifocal. A well-described familial syndrome is von Hippel–Lindau (VHL) disease, which is characterized by cerebellar hemangioblastoma, retinal angiomata, bilateral clear cell RCC, and islet cell tumors of the pancreas. Both sporadic and VHL disease types have a common genetic mechanism that includes loss of a region of chromosome 3p. Most of clear cell RCCs are believed to have loss of the VHL gene either through mutation, deletion, or silencing by methylation. Hereditary papillary RCC

(papillary type 1) is an autosomal dominant syndrome associated with abnormalities of the *MET* gene on chromosome 7. Other genetic RCC syndromes include hereditary leiomyomatosis and RCC (papillary type 2) that is associated with mutations in the Krebs cycle enzyme fumarate hydratase, and Birt–Hogg–Dubé syndrome, which manifests as bilateral multifocal tumors with both chromophobe RCC and oncocytoma histology. RCC is also associated with polycystic kidney disease, tuberous sclerosis, and acquired renal cystic disease.

Pathology

Clear cell histology is the most common RCC subtype. Most RCCs originate in the proximal tubular cells of the kidney. The tumor is multifocal in 6.5% to 10% of cases, more commonly with papillary histology. The renal capsule and Gerota fascia surrounding the kidney typically limit local extension of the tumor. The tumor cells are typically rich in glycogen and lipid, giving the tumor a clear cell appearance microscopically and a characteristic yellow appearance grossly. Less common pathologies include papillary and chromophobe RCC. Unclassified RCC is a waste-basket classification for tumors that do not fit the criteria of the classically described histologies. Sarcomatoid dedifferentiation, once believed to be a separate histologic classification, is now recognized as a dedifferentiation pathway that can occur with any RCC histology, including clear cell, papillary, and chromophobe. Oncocytoma is a benign tumor with no malignant potential that can be problematic to differentiate from chromophobe RCC on needle biopsy: both are collectively referred to as oncocytic neoplasms when a definitive diagnosis cannot be reached on the biopsy specimen.

Clinical Presentation

RCC was traditionally called the “internist’s tumor” because of its subtle presentation. Now more than 40% of clinically unsuspected tumors are found incidentally by abdominal imaging done for other reasons. Gross or microscopic hematuria, the most common presenting symptom, is present in some patients with RCC. The classic “too late” triad of hematuria, abdominal mass, and flank pain is now less frequently encountered. Paraneoplastic syndromes occur in 10% to 40% of cases and consist of fever, anemia, erythrocytosis, hypercalcemia, liver dysfunction (Stauffer

syndrome), and hypertension. Other common symptoms include bone pain and central nervous system abnormalities, due to bone and brain metastases. Risk of metastases at presentation and risk of renal mass being RCC at presentation are strongly associated with tumor size.

Diagnosis

The workup of a patient with the preceding symptoms should include a history, physical examination, complete blood cell count, serum chemistry panel (including alkaline phosphatase and liver function tests), urinalysis, urine culture, chest x-ray and a contrast-enhanced abdominal CT scan. In most cases, the CT scan will define the nature of the mass. If any of the studies obtained suggests tumor thrombus involvement of the renal vein or vena cava, an MRI or CT scan with three-dimensional reconstruction should be obtained to assess the extent of the tumor thrombus. In contrast to the management of other renal tumors, RCC may be treated surgically without preoperative histologic diagnosis of the tumor. The role of renal mass biopsy for patients who are surgical candidates, who have resectable localized tumors may be limited unless the radiographic characteristics of the mass suggest an etiology other than RCC, such as an abscess, lymphoma, urothelial carcinoma, or a metastasis from another malignant primary. Guidelines strongly recommend renal mass biopsy prior to ablation therapy or active surveillance for localized RCC, or systemic therapy (without previous histopathology) for advanced or metastatic disease.

If a mass suggests RCC, a metastatic workup consisting of a chest radiograph, CT scan (if not already obtained), and liver function tests should be performed. The most common sites of metastases of RCC in decreasing order are the lung, bone, and regional lymph nodes. If the patient does not have an increased alkaline phosphatase level or skeletal pain, a bone scan is usually not required. An MRI scan of the brain can be performed if there is any suspicion of brain metastases, and should be performed in patients who have metastatic disease elsewhere.

Grading and Staging

The most widely used grading system for RCC is the Fuhrman system, which is based on nuclear and nucleolar morphology, rated on a scale of 1 to 4.

TABLE 19.4 Staging Systems for Renal Cell Cancer

Primary Tumor Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
	T1a: Tumor ≤4 cm, confined to kidney
	T1b: Tumor >4 cm, <7 cm, confined to kidney
T2	Tumor >7 cm in greatest dimension, confined to the kidney
	T2a: Tumor >7 cm, ≤10 cm, confined to kidney
	T2b: Tumor >10 cm, confined to kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
	T3a: Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia
	T3b: Tumor grossly extends into the vena cava below the diaphragm
	T3c: Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Kidney Cancer—Anatomic Stage/Prognostic Groups

Group	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1–T2	N1	M0
	T3	N0–N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

The TNM system is most commonly used for staging in the United States (see Table 19.4).

Management

Localized/Locally Advanced Renal Cell Carcinoma

To date, surgical excision remains the only proven effective treatment of localized RCC.

There are situations in which nephron-sparing surgery is indicated for patients with RCC when feasible. For example, in cases of cT1a tumors, partial nephrectomy is the standard of care and an alternative standard for cT1b renal masses especially when there is a need to preserve renal parenchyma. Also partial nephrectomy is indicated for bilateral tumor involvement, renal insufficiency, solitary kidney, and hereditary RCC such as VHL. In this procedure, the renal artery is temporarily occluded, the kidney cooled down, and a partial nephrectomy or wedge resection performed. Gross assessment of the surgical margins is typically evaluated intraoperatively to ensure adequacy of resection. Arterial blood flow is restored after sutured reconstruction of the resection bed or renorrhaphy and approximation of renal capsule; alternatively, perirenal fat or biodegradable hemostatic material is sutured to the defect to promote healing and hemostasis. Five-year cancer-specific survival rates after partial nephrectomy for patients with stage I or II disease are approximately 90% and 80%, respectively.

Currently, partial nephrectomy constitutes the standard of care for patients with localized renal tumors less than 4 cm in size. Nephron-sparing surgery and radical nephrectomy provide equally effective curative treatments for single, small, well-localized tumors; partial nephrectomy yields 5-year cancer-specific survival rates of 92% to 97%. The incidence of tumor recurrence within the renal remnant is reported to be from 0% to 6%. Recent data also demonstrate that performing partial nephrectomy on anatomically favorable tumors between 4 and 7 cm is feasible, and when carefully performed in centers of excellence, cancer-specific survival is equivalent to those treated with radical nephrectomy. More importantly, several investigators have recently reported that radical nephrectomy is associated with a higher rate of cardiovascular complications, chronic kidney disease, noncancer mortality, and overall mortality when compared to partial nephrectomy, emphasizing the role of nephron-preserving surgery whenever feasible.

The oncologic outcome of partial nephrectomy was compared to that of radical nephrectomy in a randomized noninferiority, multicenter, controlled trial (EORTC 30904) for 541 patients with small (≤5 cm),

solitary, T1–T2 N0 M0 RCC. The study which was prematurely closed because of poor accrual, showed an intention-to-treat analysis of 10-year overall survival rates of 81.1% for radical nephrectomy and 75.7% for nephron-sparing surgery. With a hazard ratio of 1.50, the test for noninferiority was not significant (p = 0.77), and test for superiority was significant (p = 0.03). However, in RCC patients (clinically and pathologically eligible patients), the difference was even less pronounced (HR = 1.43 and HR = 1.34, respectively), and the trend in favor of radical nephrectomy was no longer significant (p = 0.07 and p = 0.17, respectively). The study concluded that both methods provided excellent oncologic results.

More recent advances in the surgical therapy of localized RCC have focused on minimally invasive strategies. Laparoscopic radical nephrectomy, performed either through standard, hand-assisted or robot-assisted approaches, has become the gold standard for the treatment of patients with localized/locally advanced RCC that is not amenable to nephron-sparing approaches. Pure laparoscopic partial nephrectomy is used in some centers, although renal reconstruction under constrains of warm ischemia times and increased risk of urologic complications have prevented this minimally invasive technique from being widely assimilated. In the last decade, robot-assisted laparoscopic partial nephrectomy has gained ground in the treatment of small renal tumors, as it is less technically challenging than the pure laparoscopic counterpart. More recent clinical research has focused on energy ablative strategies such as cryotherapy and radiofrequency ablation, either through laparoscopic or percutaneous approaches, as strategies to treat small (<4 cm) renal masses. These energy ablative strategies have recently reported encouraging intermediate term results, but data on long-term oncologic efficacy is still lacking. These modalities are considered an option for patients refusing surgery or when surgical resection is contraindicated. Thermal ablative techniques for larger cT1b tumors however, should remain investigational owning to the lack of long-term evidence on oncologic outcome. Furthermore, active surveillance of renal masses less than 3 cm has emerged as an alternative management strategy in selected patients and the elderly with severe medical comorbidities who cannot undergo surgery. A recent meta-analysis of 10 studies of active surveillance that included 331 patients with localized RCC demonstrated a metastatic progression rate of less than 2%, which is encouraging.

However, the long-term results of such approaches are still pending.

In a radical nephrectomy, the kidney, ipsilateral adrenal gland (if involved), surrounding Gerota fascia and regional lymph nodes are all resected en bloc. Although no randomized study has proved its benefit over simple nephrectomy, radical nephrectomy has the theoretical advantage of removing the lymphatics within the perinephric fat. Up to 10% of patients can have evidence of regional lymphatic metastases without distant disease, although the incidence of occult nodal involvement is in the range of 3% to 5%. The 5-year survival rates for patients with positive lymph nodes range from 8% to 35%; however, patients with papillary histology and node metastases that undergo aggressive surgical resection can enjoy an extended progression-free and overall survival, in contrast to those patients with nodal metastases from clear cell histology. Extended lymphadenectomy has never been proven to be of benefit in patients who undergo radical nephrectomy for early-stage localized RCC, except in the presence of clinically positive lymph nodes, and many surgeons prefer a limited node dissection, which has limited morbidity, for prognostic information. There are clear data that all evidence of gross disease should be removed, if feasible, at the time of nephrectomy. However, results of the EORTC randomized phase 3 trial (30881) showed a low incidence (4.0%) of unsuspected lymph node metastasis preoperatively and there were no significant differences in overall survival, time to progression of disease, or progression-free survival between patients who underwent radical nephrectomy with or without a complete lymph node dissection. NCCN guidelines recommend regional lymph node dissection for patients with palpable disease or enlarged nodes identified on preoperative imaging.

The surgical approach to radical nephrectomy is determined by the size and location of the tumor and the surgeon’s preference. A modified flank, midline, or subcostal (chevron) incision can be used. Large upper-pole tumors may be approached through a thoracoabdominal incision for greater exposure. Adrenalectomy is generally not indicated if the adrenal gland is not involved with malignancy on imaging or intraoperatively.

Approximately 15% to 20% of RCCs invade the renal vein, and 8% to 15% invade the inferior vena cava. RCC invasion of the renal vein usually does not pose a significant surgical problem. Vena caval involvement, however, may require additional extensive procedures to completely excise the tumor. Vena caval thrombi can be classified according to Mayo

classification into five levels: level 0, thrombus is within the renal vein only; level I (renal), thrombus extending into the IVC but not more than 2 cm above the renal vein; level II (infrahepatic), thrombus extending into the IVC to more than 2 cm above the renal vein but not to the hepatic vein; level III (intrahepatic), thrombus extending into the IVC to above the hepatic vein but not to the diaphragm; and level IV, thrombus extending into the supradiaphragmatic IVC or right atrium. In cases with vena caval involvement, it is imperative that the surgeon be familiar with techniques of vascular surgery, and consideration should be given to consulting with a cardiothoracic surgeon, especially for level 3–4 thrombi. Cardiopulmonary bypass, deep hypothermic arrest, and venovenous bypass have been used in the resection of these locally advanced tumors that extend to the suprahepatic vena cava.

Metastatic Renal Cell Carcinoma

Approximately 40% to 50% of patients either present with or develop metastases during the course of the natural history of their disease. The median survival for patients with metastatic RCC is 12 months. Two randomized phase 3 trials have demonstrated a significant survival benefit for patients who undergo cytoreductive nephrectomy prior to the administration of systemic interferon-alpha in those that present with metastatic disease and their primary tumor in situ. The presence of nodal metastases, in the setting of distant metastatic disease, portends a worse prognosis and a decreased likelihood of responding to systemic therapy, which may be altered by aggressive surgical resection of the nodes at the time of cytoreductive surgery.

Distant metastatic disease can be categorized as oligometastatic disease or bulky metastatic disease. Several studies have shown higher 3-year survival rates, ranging from 20% to 60%, after radical nephrectomy with removal of a solitary metastasis. Solitary lung metastases appear to be associated with better survival rates than metastases to other organ sites. Multiple metastases or multiple sites of metastases portend a significantly worse prognosis and are usually approached with systemic therapy options, although the benefit of surgical consolidation following maximum response to systemic therapy has been demonstrated in selected patients with metastatic RCC.

Cytotoxic chemotherapy has been largely ineffective in RCC; the highest objective response rate for single-agent therapy is only 16%. More

recently, regimens with gemcitabine and capecitabine have shown significant activity in selected patients. Interleukin-2 (IL-2) has yielded durable response rates of 15% to 19% in various trials, primarily with the use of high-dose bolus intravenous regimens. Subcutaneous IL-2, either alone or in combination with interferon, is believed to be inferior to intravenous IL-2 regimens, but associated with significantly less toxicity. Until recently, IL-2 was the gold standard of therapy for patients with metastatic disease, but recent inroads into the understanding of the molecular pathways associated with renal cell carcinogenesis and progression have resulted in the development of specific molecular targeted therapies that have rapidly replaced IL-2 in the armamentarium of the oncologist. Since 2005, several drugs (bevacizumab, sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, lenvatinib, temsirolimus, everolimus, nivolumab) have been approved for the treatment of metastatic RCC. The usage of these drugs depends on histology, previous treatments received and failed, and patient risk stratification. Unfortunately, these drugs, at best, only yield partial responses in some patients, with very rare instances of complete responses. A great deal of research is currently being conducted in the field of targeted therapy, with many new targeted agents in the pipeline.

TESTICULAR CANCER

Epidemiology and Etiology

Malignant tumors of the testis are rare. It has been reported that approximately 8,720 cases of testicular cancer were diagnosed in 2016, but only 380 men will die of this disease. Ninety-five percent of these tumors are of germ cell origin. Although testicular tumors can occur at any age, specific tumor types tend to occur at different ages. Choriocarcinomas tend to occur between 24 and 28 years of age, embryonal carcinomas from 26 to 34 years of age, seminomas from 32 to 42 years of age, and lymphomas and spermatocytic seminomas after the age of 50 years.

The most well-known etiologic factor in the development of testicular cancer is cryptorchidism. Between 3% and 11% of all cases of testis cancer occur in cryptorchid testes. Genetic factors may also play a significant role.

CIS (otherwise known as intratubular germ cell neoplasia) is a precursor of testicular germ cell cancer. A total of 5% to 6% of men with a unilateral

germ cell tumor have CIS in the contralateral testis, and a germ cell tumor will develop in 50% of these men. Other men with a high risk of CIS are individuals with intersex, cryptorchidism, infertility, or an extragonadal germ cell tumor.

Clinical Presentation

Testicular cancer typically presents as a painless testicular mass and/or enlargement. Advanced disease can present as back pain, flank pain, or with systemic symptoms. The differential diagnosis includes varicocele, hydrocele, hematoma, epididymitis, orchitis, and inguinal hernia.

Diagnosis

Although the diagnosis is usually evident at physical examination to an experienced clinician, scrotal ultrasound should be performed to confirm the diagnosis, evaluate local extension and assess the contralateral testis. Any solid testicular mass is considered a testicular tumor until proven otherwise. Patients with testicular enlargement that is believed to be inflammatory in nature (epididymo-orchitis) must be re-examined after the infection has been treated to rule out the presence of an occult testicular mass. Once a testicular tumor is suspected, the patient's levels of the tumor markers alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) should be tested. Following this, the patient should undergo a radical inguinal orchiectomy. There is no role for fine-needle aspiration or Tru-cut biopsy in the workup of this disease.

Before or after radical orchiectomy, staging CT scans of the chest, abdomen, and pelvis as well as postorchiectomy serum tumor markers (obtained at least 4 weeks after surgery) should be obtained in all patients for risk stratification to direct subsequent treatment. Alternatively, a chest radiograph may be obtained in patients with a low risk of thoracic metastasis such as those with normal postorchiectomy tumor markers and a normal CT of the abdomen/pelvis. Elevated serum tumor markers should be followed postorchiectomy after allowing the appropriate time for each marker to return to baseline, if possible, for precise staging. This would be approximately 1 week for hCG and 5 weeks for AFP. Preoperative sperm banking must be discussed with patients who are interested in future fertility prior to undergoing therapeutic interventions that may reduce fertility potential such as retroperitoneal lymph node dissection (RPLND),

radiation or chemotherapy.

Staging

The American Joint Committee on Cancer TNM testicular cancer staging system is outlined in Table 19.5. In terms of biologic behavior and therapy, testicular tumors can be categorized as seminomatous or nonseminomatous germ cell tumors (NSGCTs). Seminomas are radiation-sensitive and chemosensitive tumors that undergo lymphatic spread in an orderly fashion. In contrast, NSGCTs are minimally radiation sensitive and have a higher metastatic potential than seminomas.

Management

Seminomatous Germ Cell Tumors

After radical orchiectomy, the standard management options for stage I seminomas are either enrolment in active surveillance (preferred for pT1–pT3 disease) which requires a highly compliant patient, or treatment with single-agent carboplatin chemotherapy or radiation therapy to the retroperitoneal nodes up to the level of the diaphragm (doses of ~20 Gy). The cancer-specific survival for stage I seminoma is 99% irrespective of treatment modality used. Stage II seminomas are treated with radiation therapy to the retroperitoneal nodes and ipsilateral pelvic nodes up to the level of the diaphragm (doses of 30 Gy for stage IIA to 36 Gy for low-volume stage IIB). The overall survival with radiation treatment for stage II is almost 100%. Although 5% to 6% of patients with stage IIA disease have relapses, more than half of these respond successfully to salvage therapy. In contrast, cisplatin-based chemotherapy is the preferred treatment alternative for stage IIB seminoma.

Stage IIC and III diseases are usually treated with primary chemotherapy with bleomycin, etoposide, and cisplatin (BEP). Surgery is generally reserved for lymphatic disease (which is usually documented on postchemotherapy PET/CT scans) that does not respond to chemotherapy or radiation therapy and is rarely performed in the setting of metastatic seminoma following radiation and/or chemotherapy. Using this approach, 5-year disease-free survival rates of 86% and 92% have been obtained for patients with stage IIB and III diseases, respectively.

TABLE 19.5

Staging Systems for Testicular Cancer

Primary Tumor Clinical (T)

pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis and no vascular/lymphatic invasion, tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion or tumor invading into the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes masses, none more than 2 cm in greatest dimension
N2	Lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph node masses, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Lymph node mass more than 5 cm in greatest dimension

Distant Metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Presence of distant metastases M1a: Nonregional nodal or pulmonary metastases M1b: Distant metastases other than to nonregional lymph nodes and lungs

Serum Tumor Markers				
Stage	LDH	hCG (mIU/mL)		AFP (ng/mL)
SX	Marker studies not available or not performed			
S0	Marker study levels within normal limits			
S1	<1.5 × Normal	<5,000		<1,000
S2	1.5–10 × Normal	5,000–50,000		1,000–10,000
S3	>10 × Normal	>50,000		>10,000
Stage 0				
	pTis	N0	M0	S0
Stage I				
IA	pT1	N0	M0	S0
IB	pT2–T4	N0	M0	S0
IS	Any pT/TX	N0	M0	S1–S3 (postorchiectomy)
Stage II				
IIA	Any pT/TX	N1	M0	S0–S1
IIB	Any pT/TX	N2	M0	S0–S1
IIC	Any pT/TX	N3	M0	S0–S1
Stage III				
IIIA	Any pT/TX	Any N	M1a	S0–S1
IIIB	Any pT/TX	Any N	M0–M1a	S2
IIIC	Any pT/TX	Any N	M0–M1a	S3
	Any pT/TX	Any N	M1b	Any S

LDH, lactic dehydrogenase; hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein.

Nonseminomatous Germ Cell Tumors

The management strategies for stage IA disease include surveillance and nerve-sparing RPLND. While these two options are considered for stage IB NSGCT, primary systemic chemotherapy is another option to reduce the risk of relapse in these patients. Overall, approximately 20% to 30% of patients with stage I disease who undergo surveillance experience relapse. Patients at high risk of relapse include those with lymphovascular invasion or predominant embryonal histology present in the primary tumor.

The recurrence rate after RPLND for low-volume stage II disease is less than 20%. Thus, both RPLND and primary systemic chemotherapy have been used to treat low-volume retroperitoneal disease. Survival rates of 97% or better have been associated with both forms of therapy. At the MD Anderson Cancer Center, patients with stage II disease are treated with primary chemotherapy, and RPLND is used to subsequently eradicate residual disease.

Because of the high recurrence rates associated with primary RPLND

alone in patients with high-volume stage IIB, IIC, and III NSGCTs, primary systemic chemotherapy is the treatment of choice for this disease. RPLND is used to remove any residual disease that may be present after primary chemotherapy and to determine the need for further therapy. Recent experience with chemotherapy for advanced NSGCT at the MD Anderson Cancer Center has shown 5-year survival rates of 96% and 76% for low- and high-volume stage III disease, respectively.

Despite the relatively early age of onset of testicular cancer, this disease remains one of the most curable cancers. A majority of NSGCTs produce either AFP or β-hCG, rendering these markers helpful in monitoring the patient for treatment response and recurrent disease. RPLND can be performed in the primary setting (before chemotherapy, usually in stage I and IIA NSGCTs) with excellent sparing of the sympathetic nerves, and resulting preservation of ejaculatory function. RPLND in this setting is performed using modified templates (and not just simply a mass excision). For residual masses after chemotherapy (in the setting of normal markers), postchemotherapy RPLND is performed with the goal of removing any retroperitoneal lymph nodes, including any residual viable tumor or teratoma. Teratomas can be life-threatening, as they can grow very fast (growing teratoma syndrome), invade adjacent vital organs, degenerate into a sarcoma or carcinoma (somatic malignant transformation), and are resistant to chemotherapy and radiotherapy. Teratomas can only be cured by comprehensive and complete surgical excision. Typically, with postchemotherapy RPLND, a full bilateral template is performed, aiming to remove all retroperitoneal lymph nodes. Postchemotherapy RPLND is a technically challenging procedure that should only be done in experienced centers, as it is associated with higher complication rates, and could require resection of nearby involved organs (kidney, ureter, spleen, vena cava, colon) in as many as 25% of cases.

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20 Gynecologic Cancers

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INTRODUCTION

Surgical oncologists are often consulted by general obstetrician/gynecologists to assist in the management of patients with primary gynecologic malignancies. It is therefore important to understand the surgical staging procedures involved with each disease process (i.e., ovarian, fallopian tube, uterine, cervical, vulvar, and vaginal). This chapter discusses the basic principles of gynecologic oncology so appropriate management can occur when these neoplasms are unexpectedly encountered. Emphasis is placed on diagnosis, staging, and surgical management.

OVARIAN CANCER

Ovarian cancer has the highest mortality of gynecologic malignancies. Every year in the United States, approximately 22,000 new cases are diagnosed, and 14,000 women die from this disease. Ovarian cancers are heterogeneous, and subtypes are defined by histology. The most common, and "typical," subtype is epithelial ovarian cancer. Other less common subtypes are germ cell tumors and sex cord stromal tumors.

Epithelial Ovarian Cancer

Incidence and Risk Factors

Epithelial ovarian cancer occurs in 1 in 70 women and constitutes 90% of all ovarian cancers. The median age at diagnosis is 63 years. Approximately 10% of these cases are hereditary, and are transmitted in an autosomal dominant fashion. Hereditary breast ovarian cancer syndrome (BRCA-1 and BRCA-2 mutations) and Lynch syndrome/hereditary nonpolyposis colorectal cancer (in which colon, endometrial, ovarian, and other cancers cluster in first- and second-degree relatives) are known

hereditary forms of ovarian cancer. Recent next-generation sequencing efforts have identified other germline mutations that may play a role, and other genetic mutations likely remain to be identified.

Factors believed to increase the risk of a woman developing epithelial ovarian cancer are increased age (peak age is 70 years), nulliparity, early menarche, late menopause, delayed childbearing, and Ashkenazi Jewish descent. Early studies suggested an association with fertility drugs (i.e., clomiphene and gonadotropin), but subsequent studies have not confirmed this link. Both tubal ligation and salpingectomy have demonstrated a protective effect against the development of epithelial ovarian cancer, as has the use of oral contraceptives for more than 5 years.

Pathology

Tumor subtypes are listed in Table 20.1. Cases of synchronous appendiceal and ovarian mucinous tumors have also been reported, but because it is not unusual for appendiceal cancer to spread to the ovaries, it can be difficult to determine the true site of the primary disease. Endometrioid ovarian carcinomas have also been shown to have higher rates of concurrent endometrial carcinomas, though determining whether the tumors are separate primaries or represent metastatic disease can be difficult.

TABLE 20.1 Percentage Distribution of Epithelial Ovarian Carcinomas by Histologic Subtype

Histologic Subtype	Percentage Distribution
Serous	71–75
Mucinous	3
Endometrioid	8–11
Clear cell	10–12
Other (including transitional, carcinosarcoma, mixed, undifferentiated, unclassified)	2–4

Routes of Spread and Sites of Metastasis

Because exfoliated cells tend to assume the circulatory path of the peritoneal fluid and implant along this path, the most common route of metastasis is by seeding. Epithelial ovarian cancer may also metastasize to

the lymph nodes. Hematogenous spread is uncommon.

Clinical Features

Symptoms. The interval from onset of disease to diagnosis is often prolonged because of lack of specific symptoms; nonspecific symptoms include persistent urinary and abdominal problems. The diagnosis is often not made until patients have disseminated disease, with more than 70% of cases presenting at stage III or IV. Patients with stage IV disease and malignant pleural effusions may present with a cough or shortness of breath. It is uncommon for ovarian cancer to be diagnosed by abnormal Papanicolaou (Pap) smear results.

Physical Findings. An adnexal mass noted on routine pelvic examination and a palpable fluid wave are often found in patients with advanced-stage epithelial ovarian cancer. About 5% of patients with presumed ovarian cancer have another primary tumor that has metastasized to the ovary, though some estimates suggest up to 30% may be metastases from other sites. The most common primary cancers that metastasize to the ovary are breast, gastrointestinal tract, and other gynecologic cancers.

Pretreatment Workup

Careful physical examination, including pelvic examination with rectovaginal examination, is required. Pretreatment workup also includes clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function, serum albumin, and CA-125 [which is elevated in approximately 80% of cases]), chest radiography, and mammography. Computed tomography (CT) analysis may help determine the extent of disease. Colonoscopy is useful in examining the colon and can be particularly helpful in distinguishing between a primary ovarian and primary colon cancer, which may present in the same way.

Staging

The surgical staging schema for epithelial ovarian cancer is outlined in Table 20.2.

Treatment

Traditionally, the initial step in treatment is surgical cytoreduction with

appropriate intraoperative staging procedures, including abdominal and pelvic cytologic analysis (or collection of ascites), careful exploration of all abdominal and pelvic structures and surfaces, total abdominal hysterectomy and bilateral salpingo-oophorectomy (except in cases of concern about fertility or of early-stage disease), omentectomy, and selective pelvic and para-aortic lymph node sampling. In patients with a mucinous tumor or an involved appendix, appendectomy should be performed. Primary cytoreduction is a key component in advanced cases because survival is inversely correlated to the amount of residual tumor remaining. In the past, optimal tumor reductive surgery was defined as the diameter of the largest residual tumor implant being less than 1 cm. However, there has been a recent movement to update the definition of optimal tumor reductive surgery to no visible residual disease, as studies suggest outcomes are significantly better in this population.

TABLE 20.2 Surgical Staging of Epithelial Ovarian Cancer or Fallopian Tube Cancer

Tumor Stage	Description
I	Tumor limited to the ovaries [or fallopian tubes]
IA	Tumor limited to one ovary [or fallopian tube], negative washings, no tumor on the external ovarian surfaces, intact capsule
IB	Tumor in both ovaries, negative washings, no tumor on the external surfaces, intact capsules
IC1	Tumor in one or both ovaries [or fallopian tubes], with intraoperative rupture or surgical spill
IC2	Tumor in one or both ovaries [or fallopian tubes], capsule rupture before surgery or tumor present on external ovarian surfaces
IC3	Tumor in one or both ovaries [or fallopian tubes], malignant ascites or malignant cells in peritoneal washings
II	Tumor involving one or both ovaries [or fallopian tubes] with pelvic extension; primary peritoneal cancer is considered at least stage II
IIA	Extension and/or metastases to the uterus and/or fallopian tubes [and/or ovaries]
IIB	Extension to other pelvic tissues
III	Tumor involving one or both ovaries [or fallopian tubes] with spread outside the pelvis and/or positive retroperitoneal lymph nodes; tumor limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum; superficial liver metastasis are included in stage III
IIIA1(i)	Extrapelvic spread that only involves retroperitoneal lymph nodes, ≤10 mm in size
IIIA1(ii)	Extrapelvic spread that only involves retroperitoneal lymph nodes, >10 mm in size
IIIA2	Macroscopic peritoneal involvement outside of the pelvis above the pelvic brim, with or without positive retroperitoneal lymph nodes
IIIB	Histologically confirmed implants of abdominal peritoneal surfaces ≤2 cm in diameter, with or without involvement of the retroperitoneal lymph nodes; includes extension to the capsule of liver or spleen
IIIC	Abdominal implants >2 cm in diameter with or without positive retroperitoneal or inguinal nodes; includes extension to the capsule of liver or spleen
IV	Tumor involving one or both ovaries [or fallopian tubes] with distant metastases; positive cytologic results from pleural effusion or pathologic confirmation of parenchymal liver metastases
IVA	Pleural effusion with positive cytology
IVB	Hepatic or splenic parenchymal metastasis, or metastasis to other organs outside of the abdomen; includes inguinal lymph nodes and lymph nodes outside of the abdomen

In select cases, there may be a role for neoadjuvant (upfront) chemotherapy followed by an interval cytoreduction procedure. In patients with advanced cancer, neoadjuvant chemotherapy may be warranted for

those with multiple medical comorbidities that preclude aggressive surgical debulking or extensive disease that cannot be optimally reduced (as determined by CT scan, laparotomy, or diagnostic laparoscopy). Although no definitive conclusion has been reached, several large, prospective trials have demonstrated noninferiority when comparing neoadjuvant to adjuvant chemotherapy with debulking in patients with stage IIIC and IV disease. Studies are ongoing to determine which patients, if any, would benefit most from neoadjuvant chemotherapy.

After surgical cytoreduction, patients should be treated with combination platinum- and taxane-based chemotherapy. Bevacizumab may also be considered in this setting. The addition of bevacizumab has been associated with a progression-free survival benefit, though no overall survival benefit in optimally debulked patients has been demonstrated. After six to eight courses of chemotherapy, treatment decisions are based on the presence of persistent disease or the disease-free interval. Following treatment, imaging studies are now used to determine treatment response. "Second-look" laparotomy or laparoscopy is no longer routinely used.

Prognostic Factors

Prognostic pathologic factors include tumor grade (low or high grade), histologic subtype, and DNA ploidy. Clinical factors of prognostic significance include surgicopathologic stage, extent of residual disease remaining after primary cytoreduction (Tables 20.3 and 20.4), volume of ascites, patient age, and patient performance status. Patients with poor performance status before treatment have significantly shorter survival than do patients with good performance status.

TABLE 20.3 Five-Year Survival Rates for Patients with High-Grade Epithelial Ovarian Cancer, by Tumor Stage and Amount of Residual Disease[a]

Tumor Stage	Survival (%) High Grade
I	90
IA	94
IB	92
IC	85
II	70
IIA	78
IIB	73
III	39
IIIA	59
IIIB	52
IIIC	39
IV	20

Prognosis Based on Residual Disease following Primary Cytoreductive Surgery	
Amount of Residual Disease	**Medial Overall Survival**
Microscopic (residual disease)	70–86 months
Macroscopic (optimal debulking)	40–46 months
Macroscopic (suboptimal debulking)	39 months

[a]Based on prior staging system; most recent staging system was developed in 2014 so data are not yet mature.

TABLE **20.4** Ten-Year Survival and Median Survival Rates for Low-Grade Ovarian Cancer by Tumor Stage

Stage	10-Year Survival (%)	Median Survival
I	92	123 months
II–IV	55	82–97 months

Recommended Surveillance

Patients should be followed every 3 to 4 months for the first 2 years, every 6 months for years 3 to 5, and then annually after 5 years. A physical examination with pelvic examination should be performed at each visit, and the option of monitoring CA-125 levels should be discussed with the patient. As clinically indicated, a CT of the chest, abdomen and pelvis, +/− a PET component can be performed.

Ovarian Tumors of Low Malignant Potential

Incidence and Risk Factors

Sometimes referred to as borderline tumors, ovarian tumors of low malignant potential (LMP) constitute as many as 10% to 20% of epithelial ovarian malignancies. The highest incidence is among white women, and the median age at diagnosis is 40 to 50 years (approximately 10 to 20 years younger than that for epithelial ovarian cancer). No risk factors have been identified, and pregnancy and exogenous hormones do not appear to be protective. There is no apparent association with family history.

Pathology

The most common histologic subtypes of ovarian tumors of LMP are serous and mucinous (Table 20.5). Diagnosis requires the absence of frank stromal invasion. Distinct pathologic features that may be associated with a more aggressive disease course include micropapillary architecture, microinvasion, and invasive implants.

Clinical Features

Patients with ovarian tumors of LMP, as well as those with epithelial ovarian cancers, present similarly. The most common symptoms are lower abdominal pain or discomfort, early satiety, dyspepsia, and a sense of abdominal enlargement. Ovarian tumors of LMP can also be identified as an adnexal mass on routine pelvic examination. The CA-125 levels may be elevated in serous tumors.

Treatment

In contrast to patients with invasive epithelial ovarian cancer, the vast majority of patients with borderline ovarian tumors are diagnosed with early-stage disease. Recommended treatment for all patients is primary surgery; fertility-sparing procedures should be performed in patients with stage I disease who desire children in the future. There has been no proven benefit to adjuvant therapy in treating this cancer, even in patients with advanced-stage disease. Typically, these tumors have an indolent clinical course and may recur after a long disease-free interval. Tumor stage is the most important predictor of survival (Table 20.6). Secondary cytoreduction can be considered in select patients with recurrent disease.

TABLE

Distribution of Ovarian Tumors of Low Malignant

TABLE 20.5 Potential, by Tumor Stage and Histologic Type

Tumor Stage	Histologic Type	
	Serous (%)	Mucinous (%)
I	65	90
II	14	1–2
III	20	5–10
IV	1	1

TABLE 20.6 Five-Year Survival Rates for Patients with Ovarian Tumors of Low Malignant Potential, by Tumor Stage

Tumor Stage	Survival Rate (%)
I	>95
II	77–98
III	74–96
IV	77

Ovarian Germ Cell Tumors

Incidence and Risk Factors

Germ cell tumors are the second most common type of ovarian tumor. Among women 20 years of age or younger, up to 75% of ovarian tumors are of germ cell origin, and up to one-third of these are malignant. The mean age at diagnosis is 19 years; germ cell tumors rarely occur after the third decade of life. Sixty to 75% of cases are stage I at diagnosis.

Pathology

The histologic subtypes of germ cell tumors and their incidences are listed in Table 20.7.

TABLE 20.7 Clinical Features of Ovarian Germ Cell Tumors, by Histologic Subtype

Histologic Subtype	Incidence (%)	Tumor Markers			Other Notes
		AFP	β-hCG	LDH	
Dysgerminoma	34–40	–	–	±	May be bilateral in 10–15% of cases
Endodermal sinus tumor	14–22	±	–	±	
Immature teratoma	20–36	±	–	±	
Embryonal carcinoma	1–4	±	±	–	
Choriocarcinoma	1–3	–	+	–	
Polyembryonal	1–3	±	±	–	
Mixed tumor	5–15	±	±	±	Clinical characteristics depend on components present

AFP, α-fetoprotein; β-hCG, beta subunit of human chorionic gonadotropin; LDH, lactic dehydrogenase; +, positive result; –, negative result; ±, positive/negative result.

Routes of Spread and Sites of Metastasis

Germ cell tumors have the same potential as epithelial ovarian tumors to metastasize.

Clinical Features

Germ cell malignancies grow rapidly and are often characterized by pain secondary to torsion, hemorrhage, or necrosis. They may also cause mass effects including bladder or rectal complaints, or menstrual abnormalities. Dysgerminomas account for up to 20% to 30% of malignant ovarian tumors diagnosed during pregnancy. Embryonal carcinomas may produce estrogen and cause precocious puberty.

Pretreatment Workup

Careful physical examination, including pelvic examination, is required. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function, serum albumin) and chest radiography. Serum markers, including α-fetoprotein, β-human chorionic gonadotropin (β-hCG), and lactic dehydrogenase, should be measured (Table 20.7). Premenstrual women with an ovarian mass should undergo karyotyping because the incidence of dysgenic gonads is increased in patients with these tumors.

Staging

The surgical staging criteria are the same as those for epithelial ovarian cancer (Table 20.2).

Treatment

In general, surgical staging includes unilateral salpingo-oophorectomy (if there is a desire to preserve fertility), peritoneal cytology, omentectomy, and selective biopsies of retroperitoneal lymph nodes and abdominal structures. For patients whose disease is inadequately staged, there are two options: surgical re-exploration and appropriate staging, and initiation of chemotherapy without re-exploration. In most cases, it is unnecessary to delay chemotherapy by re-exploration and staging because these tumors are highly chemosensitive.

Chemotherapy is recommended for all patients with germ cell tumors, although chemotherapy for those with stage I tumors does remain controversial. Chemotherapy should begin 7 to 10 days after surgical exploration because of rapid tumor growth. The first-line regimen is bleomycin, etoposide, and cisplatin administered for three or four cycles in 21-day intervals. Radiotherapy may have a limited role in the treatment of dysgerminomas.

Prognostic Factors

The survival rates for individual ovarian germ cell tumor subtypes are listed in Table 20.8. Prognostic factors for immature teratomas include tumor grade, extent of disease at diagnosis, and amount of residual tumor. The tumor grade of immature teratomas is determined by the extent of immature tissue present. Older age has been associated with increased risk of recurrence in dysgerminomas. Tumor stage is also an important prognostic factor for all ovarian germ cell tumors (Table 20.9).

Recommended Surveillance

Patients should be followed up every 3 to 4 months for the first 2 years, and then annually. A physical examination with pelvic examination should be performed at each visit. Labs (e.g., CA-125, α-fetoprotein, β-hCG, and lactic dehydrogenase) should be checked if they were initially elevated. As clinically indicated, a CT of the chest, abdomen, and pelvis, +/− a PET/CT scan can be performed.

TABLE 20.8 Five-Year Survival Rates for Patients with Most Common Ovarian Germ Cell Tumors, by Histologic Subtype and Tumor Stage

Histologic Subtype and Tumor Stage or Grade	Survival Rate (%)
Dysgerminoma	
Overall	80–98
Stage I	90–95
Endodermal sinus tumor	
Overall	70
Stages I and II	75–95
Immature teratoma	
Overall	90–100
Stage I	90–100

Sex Cord Stromal Tumors

Incidence and Risk Factors

Sex cord stromal tumors account for 5% to 8% of ovarian malignancies and up to 5% of childhood malignancies. Occurrence before menarche is often associated with precocious puberty.

Pathology

As their name suggests, these tumors are derived from sex cords or stroma. Derivatives include granulosa cells, theca cells, stromal cells, Sertoli cells, Leydig cells, and cells resembling embryonic precursors of these cell types.

Routes of Spread and Sites of Metastasis

The pattern and sites of metastatic spread are analogous to that of epithelial ovarian cancers.

Clinical Features

Fibromas and Fibrosarcomas. Fibromas and fibrosarcomas are the most common sex cord stromal tumors and constitute 4% of ovarian neoplasms. The mean age at diagnosis for fibromas is in the fifth decade of life. Ten percent of these lesions are bilateral. Symptoms include ascites especially in patients with tumors larger than 6 cm in diameter, increased abdominal girth, Meigs syndrome (right pleural effusion and ascites), and Gorlin

syndrome with basal nevi. These tumors are primarily inert but may secrete small amounts of estrogen.

Granulosa Cell Tumors . Granulosa cell tumors comprise 1% to 2% of ovarian tumors. Adult-type tumors (90% to 95% of granulosa cell tumors) are characterized by secretion of excess estrogen. Patients may experience menstrual irregularities or postmenopausal bleeding. Five to 15% of patients present with an acute abdomen caused by tumor hemorrhage. Patients with juvenile-type granulosa cell tumors (5% to 10% of granulosa cell tumors) can also present with abnormal uterine bleeding and abdominal pain. Because granulosa cell tumors produce estrogen, coexisting endometrial pathologic processes occur in approximately 30% of patients. In rare cases, these tumors may produce testosterone and cause some virilizing features.

TABLE **20.9** Five-Year Survival Rates for Patients with Ovarian Germ Cell Tumors, by Tumor Stage

Tumor Stage	Survival Rate (%)
I	98
II	94
III	87
IV	69

Thecomas . Thecomas are rarer than granulosa cell tumors, but also produce estrogen. The mean age at diagnosis is around 50 years, and these tumors are rarely bilateral. Menstrual abnormalities and postmenopausal bleeding are the most common presenting symptoms.

Sertoli Cell Tumors . The average age at diagnosis of Sertoli cell tumors is approximately 30 years, but these tumors can occur at any age. Sertoli cell tumors are unilateral. Patients more frequently have symptoms related to excess estrogen, though may exhibit signs of virilization. Rarely, hyperaldosteronemia manifested as hypertension and hyperkalemia may develop. Seventy percent of these tumors produce both estrogen and androgens, whereas 20% produce androgens alone.

Leydig Cell Tumors . Leydig cell tumors occur at an average age of 50

to 70 years but can occur at any age. These tumors are often unilateral. Symptoms often include signs of virilization or postmenopausal bleeding due to a propensity to produce androgens and/or estrogen.

Sertoli–Leydig Cell Tumors . Sertoli–Leydig cell tumors can occur at any age, but 75% occur before age 40. These tumors are rarely bilateral. Most of these tumors produce testosterone, and virilization may occur in up to 85% of patients.

Gynandroblastomas . Gynandroblastomas are rare tumors with a mean age of diagnosis of 30 years. Histologically, both granulosa cell and Sertoli–Leydig cell components may be present in these tumors. Patients may experience estrogenic effects or virilization secondary to the hormone products of these tumors. These tumors may produce androgens or estrogen, or they may be inert.

Sex Cord Tumors with Annular Tubules . The average age of patients with sex cord tumors with annular tubules is 25 to 35 years. These tumors may be associated with Peutz–Jeghers syndrome, and in these cases, 66% are bilateral and most produce estrogen. These tumors are also associated with endocervical adenocarcinomas.

Pretreatment Workup

Careful physical examination, including pelvic examination, is required. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function, serum albumin, CA-125), chest radiography, and mammography. Evaluation of serum concentrations of estradiol, dehydroepiandrosterone, testosterone, 17-OH-progesterone, and hydrocortisone may be helpful in diagnosis. CT and ultrasonography should be performed to evaluate the adrenal glands and ovaries. Although imaging studies may be helpful, they do not often change the planned staging procedure.

Staging

The surgical staging criteria are the same as those for epithelial ovarian cancer (Table 20.2).

Treatment

In general, surgical staging of sex cord stromal tumors can be accomplished by unilateral salpingo-oophorectomy (if there is a desire to maintain fertility), peritoneal cytology, infracolic omentectomy, selective biopsies of nodes and abdominal structures, and appropriately targeted biopsies. If a hysterectomy is not performed at the time of surgery, dilatation and curettage and endocervical curettage should be performed to evaluate any coexistent pathologic processes.

TABLE 20.10 Five-Year Survival Rates for Patients with Sex Cord Stromal Tumors, by Histologic Subtype

Histologic Subtype	Survival Rate (%)
Granulosa cell tumor	
Stage I	90–100
Stage II–IV	30–80
Sertoli–Leydig	
Stage I	92
Stage II–IV	33

Tumors of stromal origin (i.e., thecomas and fibromas) and Leydig cell tumors generally follow a benign course; surgery is the only treatment. Sertoli cell or granulosa cell tumors are generally of LMP, tend to recur late, and rarely metastasize. Postoperative adjuvant therapy with bleomycin, etoposide, and cisplatin or other platinum-based chemotherapy should be considered in patients with disease greater than stage I or recurrent tumors, or higher-risk stage I tumors such as those with heterologous elements or that are poorly differentiated. Pelvic radiation therapy can also play a role in the treatment of these patients.

Prognostic Factors

Younger age and earlier stage are associated with better survival outcomes. Survival rates are described in Tables 20.10 and 20.11.

Recommended Surveillance

Patients should be followed up every 3 to 4 months for the first 2 years, then every 6 months following. A physical examination with pelvic examination should be performed at each visit. Current recommendations suggest that there is insufficient data to support routine use of serum tumor

markers, but some clinicians will monitor labs if they were initially elevated at each visit. As clinically indicated, a CT of the chest, abdomen and pelvis, +/− a PET component can be performed.

Management of Incidental Cancers Found at Laparotomy

The finding of an unsuspected ovarian mass at the time of exploratory laparotomy or at laparotomy for an unrelated condition can pose a therapeutic dilemma to the surgeon. Appropriate treatment depends on several factors, including the patient's age, the size and consistency of the mass, possible bilaterality, and gross involvement of other structures. Informed consent is a key component to the decision-making. Unless there is a life-threatening situation, a hysterectomy and bilateral salpingo-oophorectomy should be performed only with proper informed consent, especially in women of childbearing age.

TABLE 20.11 Five-Year Survival Rates for All Patients with Sex Cord Stromal Tumors

Stage	Survival Rate (%)
I	95
II	78
III	65
IV	35

Ovarian Mass in Premenopausal Women: Functional Cysts

An unsuspected mass in a young patient is most likely benign. The most frequently found benign masses involving the adnexa are functional cysts, which are related to the process of ovulation. These cysts are significant because they cannot be easily distinguished from true neoplasms on clinical grounds alone. The corpus luteum, which is formed during ovulation, may become abnormally large if there is hemorrhage within it. A patient with a hemorrhagic corpus luteum may present with an acute abdomen, which necessitates surgery. Often the bleeding area may be oversewn without the need for removal of the cyst, fallopian tube, or ovary. Resolution of incidentally found simple cysts up to 5 cm can be evaluated with physical examination alone or in conjunction with pelvic ultrasonography.

Other Common Masses . Other common ovarian masses found in premenopausal women are listed in Table 20.12. Masses may be asymptomatic, but if large enough may cause abdominal or pelvic pain. Ovarian torsion may occur with ovarian masses, and commonly occurs in children, young women, and pregnant women. Severe acute abdominal pain is usually the initial symptom, and this condition constitutes a surgical emergency. If a patient is hemodynamically stable, a diagnostic laparoscopy should be considered.

TABLE 20.12 Benign Ovarian Masses in Premenopausal Women

	Symptoms	Treatment	Other Notes
Functional cyst	Usually asymptomatic	Conservative management, especially if <5 cm in diameter	Extremely common, can occur with normal ovulation and usually resolve spontaneously
Dermoid cyst	May be asymptomatic; if large may have pelvic pain, possibility of ovarian torsion	Cystectomy or unilateral oophorectomy with close inspection of the contralateral ovary; attempt to retain normal-appearing ovarian tissue	15% are bilateral
Cystadenoma	May be asymptomatic; if large may have pelvic pain, possibility of ovarian torsion	Unilateral oophorectomy (if other ovary appears normal)	Serous or mucinous histology
Endometrioma	Often have a history of pelvic pain related to endometriosis	Possible cystectomy or unilateral oophorectomy; attempt to retain normal-appearing ovarian tissue	Endometriotic lesions may be visible in the abdomen

Treatment

If ascites is present on opening of the abdomen, it should be evacuated and

submitted for cytologic analysis. After careful inspection and palpation, if the ovarian mass appears to be confined to one ovary and malignancy is suspected, unilateral salpingo-oophorectomy is appropriate in most circumstances. If the mass is believed to be benign, ovarian cystectomy may be preferable. The ovarian capsule should be inspected for any evidence of rupture, adherence, or excrescence. Once removed, the ovarian specimen should be sent for frozen-section examination. If malignancy is diagnosed, surgical staging should be performed. This should include biopsies of the omentum, peritoneal surfaces of the pelvis and upper abdomen, and retroperitoneal lymph nodes (including both the para-aortic and the bilateral pelvic regions).

If the contralateral ovary appears normal, random biopsy or wedge resection is not indicated because it may interfere with future fertility due to peritoneal adhesions or ovarian failure. If the histologic diagnosis is questionable based on frozen-section results, it is always preferable to wait for permanent section results before proceeding with a hysterectomy and bilateral salpingo-oophorectomy in a young patient. General criteria for conservative management include young patients desirous of future childbearing; patient and family consent and agreement to close follow-up; no evidence of dysgenetic gonads; any unilateral malignant germ cell, stromal, or borderline tumor; and stage IA invasive epithelial tumor.

Advances in assisted reproduction have greatly influenced intraoperative management decisions. Traditionally, if a bilateral salpingo-oophorectomy is indicated, a hysterectomy has also been performed. Current technology for donor oocyte transfer and hormonal support, however, allows a woman without ovaries to sustain a normal intrauterine pregnancy. Similarly, if the uterus and one tube and ovary are removed because of tumor involvement, current techniques allow for retrieval of oocytes from the patient's remaining ovary, in vitro fertilization with sperm from her partner, and implantation of the embryo into a surrogate.

Ovarian Mass in Postmenopausal Women . The risk of an ovarian mass being malignant begins to increase at 40 years of age and rises steadily thereafter. Therefore, the finding of an unsuspected ovarian mass in a postmenopausal woman is more ominous. The most common malignant neoplasms in this age group are malignant epithelial tumors; germ cell and stromal cell tumors rarely occur. Benign lesions, such as epithelial cystadenomas and dermoid cysts, can still occur in this

population, although they do so much less frequently than in younger patients. Treatment of an unanticipated ovarian mass in a postmenopausal patient includes salpingo-oophorectomy and further staging if the frozen section reveals a diagnosis of cancer. Appropriate staging biopsies should also be performed. A gynecologic oncologist should be consulted.

Laparoscopy for the Management of Ovarian Cancer

Laparoscopy has been widely used as the standard surgical approach for benign and suspicious adnexal masses. The role of laparoscopy in the treatment of ovarian cancer is less clear, but some studies have suggested that it can be used safely at the time of surgical staging for patients with early ovarian cancer. The role of laparoscopy in treating patients with advanced ovarian cancer still needs to be defined, although laparoscopic surgery is associated with significantly less morbidity than laparotomy.

FALLOPIAN TUBE CANCER

Incidence and Risk Factors

Fallopian tube cancer accounts for less than 2% of gynecologic malignancies. The average age at diagnosis is 55 years.

Pathology

The most common histologic subtype is adenocarcinoma, and the most common tumors of the fallopian tube are metastatic lesions from other sites. To establish a diagnosis of primary fallopian tube cancer, Hu's criteria must be met: The main tumor must be in the fallopian tube, the mucosa should be involved microscopically and exhibit a papillary pattern, and the transition between benign and malignant tubal epithelium should be demonstrated if the tubal wall is significantly involved with the tumor.

Routes of Spread and Sites of Metastasis

Fallopian tube cancer metastasizes in a manner similar to that of epithelial ovarian cancer. Lymphatic spread tends to play more of a role in fallopian tube cancer. Because of the presence of extensive lymphatics, one-third of patients exhibit evidence of nodal metastases.

Clinical Features

The classic triad of primary fallopian tube cancer is watery vaginal discharge, pelvic pain, and a pelvic mass. However, this triad is present in less than 15% of patients. Watery discharge and vaginal bleeding are the most commonly reported symptoms.

Pretreatment Workup

Careful physical examination, including pelvic examination, is required. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function, serum albumin, and CA-125), chest radiography, and mammography. Imaging studies may be helpful but usually do not change the planned staging procedure. CT may help determine the extent of disease. Colonoscopy is useful in examining the colon. It can also be particularly helpful in distinguishing a colonic primary in older patients from either fallopian tube or ovarian cancer, which may present with similar symptoms.

Staging

The International Federation of Gynecology and Obstetrics (FIGO) staging system for fallopian tube cancer is similar to that of ovary, and is listed in Table 20.2.

Treatment

Treatment of fallopian tube cancer is analogous to that of epithelial ovarian cancer.

Prognostic Factors

It is difficult to determine the prognostic factors specific to fallopian tube cancer because this disease is rare, but they are likely similar to those of epithelial ovarian cancer. Some studies suggest that overall survival may be slightly better in fallopian tube cancer than epithelial ovarian cancer, even when patients have advanced disease at presentation.

Recommended Surveillance

Recommended surveillance is the same as for epithelial ovarian cancer.

UTERINE CANCER

Cancers of the uterus are divided into three main categories: those arising

from the endometrium (endometrial cancer), those arising from the myometrium or muscle layer (uterine sarcomas), and those associated with pregnancy (gestational trophoblastic disease).

Endometrial Cancer

Incidence and Risk Factors

Endometrial cancer is the most common malignancy of the female genital tract and the fourth most common cancer among women in the United States (following breast, lung, and colon cancers). Approximately 60,000 new cases are diagnosed annually and approximately 10,000 women die yearly from this disease. The median age at diagnosis is 61 years, although up to 25% of patients are premenopausal at the time of diagnosis. Approximately 3% of cases of endometrial cancer are hereditary. Lynch syndrome/hereditary nonpolyposis colorectal cancer is a hereditary cancer predisposition syndrome characterized by the development of multiple cancers, including endometrial, colorectal, and ovarian cancer. Other risk factors for endometrial cancer include obesity, nulliparity, early menarche, late menopause, unopposed estrogen therapy, and chronic diseases such as diabetes mellitus and hypertension.

Pathology

Up to 90% of endometrial cancers are endometrioid adenocarcinomas (approximately 15% of these are grade 3), with the remaining being primarily papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas (previously called malignant mixed mullerian tumors). The latter three histologic subtypes are more aggressive, accounting for a largely disproportionate number of the recurrences and deaths due to endometrial cancer.

Routes of Spread and Sites of Metastasis

Endometrial cancer metastasizes primarily by myometrial invasion and direct extension to adjacent structures, including the cervix, vagina, and adnexa. Lymphatic embolization and hematogenous dissemination can also occur.

Clinical Features

Patients commonly present complaining of abnormal uterine bleeding or postmenopausal bleeding; approximately 15% of patients with

postmenopausal bleeding have uterine cancer. Patients may also experience pelvic pressure and pelvic pain. Other associated findings include abnormal vaginal discharge, heavy menses, intermenstrual bleeding, and, in some cases, an abnormal Pap smear result. The presence of atypical glandular cells on a Pap smear requires that an endometrial biopsy be performed to rule out malignancy.

Pretreatment Workup

Careful physical examination, including pelvic examination, is required. Pathologic confirmation of the disease by endometrial biopsy or dilatation and curettage is essential. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, and CA-125) and chest radiography. Diagnostic tests, including CT or magnetic resonance imaging (MRI) should be performed as indicated by symptom examination findings or preoperative histology evaluation.

Staging

The surgical staging schema for endometrial cancer is described in Table 20.13. The FIGO grading schema is based on both architecture and nuclear appearance (Table 20.14).

Treatment

Unless a patient has comorbidities that do not allow for surgical intervention, hysterectomy, abdominal exploration via laparotomy or laparoscopy, and possibly bilateral salpingo-oophorectomy are the standard treatment for patients with endometrial cancer. Additional surgical staging biopsies, omentectomy, and lymph node dissection are also recommended in certain cases. Low-risk patients with grade 1 or 2 endometrioid adenocarcinoma with myometrial invasion of <50% with a primary tumor diameter of <2 cm do not benefit from lymphadenectomy. Furthermore, if lymphadenectomy is performed in high-risk patients (i.e., those with high grade tumors or deep myometrial invasion), a systematic clearance of lymph nodes in the pelvis and para-aortic regions is recommended. Recently, sentinel lymph node biopsy has been studied as a less morbid alternative to full lymphadenectomy, and is currently under evaluation in both low- and high-risk subgroups.

TABLE 20.13 Surgical Staging of Endometrial Cancer

Tumor Stage	Description
I	Tumor confined to the uterine corpus
IA	Tumor confined to the uterus, no or <½ myometrial invasion
IB	Tumor confined to the uterus, ≥½ myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
III	Extension of the tumor outside the uterus but confined to the true pelvis or para-aortic area
IIIA	Tumor invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IV	Distant metastases or involvement of adjacent pelvic organs
IVA	Tumor invasion of the bowel or bladder mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal lymph nodes

Up to 25% of premenopausal patients with endometrial cancer have a synchronous or metastatic ovarian malignancy, so in young patients who want to preserve their ovarian function, the ovaries should be carefully inspected at the time of exploration. After surgical management, adjuvant chemotherapy, radiation, or both may be indicated. For patients at risk for pelvic or vaginal cancer recurrence, whole pelvic radiotherapy and/or vaginal brachytherapy has been shown to decrease local recurrence. However, adjuvant radiation has not been shown to improve overall survival.

TABLE 20.14 International Federation of Gynecology and Obstetrics Grading of Endometrial Cancer

Tumor Grade	Description
1	Well-preserved glandular morphology, <5% of the tumor has a nonsquamous or nonmorular solid growth pattern; nuclei are uniform round or oval with even distribution of chromatin and inconspicuous nucleoli
2	5–50% of the tumor has a nonsquamous or nonmorular solid growth pattern; nuclei are irregular and oval-shaped, with chromatin clumping and moderate-size nucleoli
3	>50% of the tumor has a nonsquamous or nonmorular solid growth pattern; nuclei are large and pleomorphic with coarse chromatin and large irregular nucleoli

TABLE **20.15** Five-Year Survival Rates for Patients with Endometrial Cancer, by Tumor Stage

Tumor Stage	Survival Rate (%)
IA	88
IB	75
II	69
IIIA	58
IIIB	50
IIIC	47
IVA	17
IVB	15

In those patients whose comorbidities preclude surgery, or those patients who desire future fertility, local or high-dose systemic progesterone treatment may be effective. Frequent surveillance with endometrial sampling is recommended in these patients. Estrogen antagonists, aromatase inhibitors, and progestational agents with a more tolerable side effect profile when compared to conventional chemotherapy, may have a role in the treatment of recurrent and advanced disease.

Prognostic Factors

Tumor stage is the most important prognostic variable for endometrial cancer (Table 20.15). Other prognostic factors are myometrial invasion, lymphovascular space invasion, nuclear grade, histologic subtype, tumor size, patient age, hormone receptor status, and type of primary treatment used (surgery vs. radiation therapy).

Recommended Surveillance

Physical and pelvic examinations should be performed every 3 to 6 months in the first 2 years after diagnosis depending on risk status, every 6 months in years 3 to 5, and annually thereafter. Routine Pap smears and imaging during surveillance are not recommended as there is no evidence to show benefit in outcome.

Uterine Sarcomas

Incidence and Risk Factors

Uterine sarcomas account for approximately 5% of uterine cancers. Most patients have no known risk factors. A small number of patients have a history of pelvic irradiation. Though exact rates vary, less than 1% of hysterectomies performed for benign indications contain an occult sarcoma.

Pathology

Uterine sarcomas arise from mesodermal derivatives that include uterine smooth muscle, endometrial stroma, and blood and lymphatic vessel walls. The number of mitoses per 10 high-power fields, the degree of cytologic atypia, and the presence of coagulative necrosis are the most reliable predictors of biologic behavior. This disease is classified according to the type of elements involved (pure, only mesodermal elements present and mixed, both mesodermal and epithelial elements present) and whether malignant mesodermal elements are normally present in the uterus (homologous, only smooth muscle and stroma present and heterologous, striated muscle and cartilage present). The most common histologic subtypes are leiomyosarcomas (approximately 60%) and endometrial stromal sarcomas (up to 20%). Less common subtypes are adenosarcomas, pure heterologous sarcomas, and other variants.

TABLE 20.16 Clinical Features of Uterine Sarcomas and Basis for Pathologic Confirmation of the Disease, by Histologic Subtype

Histologic Subtype	Patient's Age	Signs and Symptoms	Other Notes
Endometrial stromal sarcoma	40–55 years	Vaginal bleeding	Low grade most common, high grade and undifferentiated are less common
		Lower abdominal pain or pressure	Low-grade tumors may be sensitive to hormones, and as such patients may benefit from oophorectomy
		Enlarged uterus May be asymptomatic	
Leiomyosarcoma	45–55 years	Vaginal bleeding	May be misdiagnosed as fibroids on imaging and only discovered on surgical pathology evaluation
		Pelvic mass Lower abdominal pain or pressure	
Adenosarcoma	Average age is 58 years, but can be premenopausal as well	Vaginal bleeding	Often relatively large, polypoid tumors, may be visible protruding from cervix on examination
		Uterine enlargement	

Routes of Spread and Sites of Metastasis

Sarcomas demonstrate a propensity for early hematogenous dissemination and lymphatic spread. Metastasis is exhibited in one-third of patients.

Pretreatment Workup

Careful physical examination, including pelvic examination, is required. Clinical features of uterine sarcomas are listed in Table 20.16. Endometrial biopsy, dilatation and curettage, or both are essential to providing pathologic confirmation of disease. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, and liver function), and chest

radiography. Diagnostic tests, including CT or MRI should be performed as indicated by symptoms examination findings, or preoperative histology evaluation.

Staging

In 2009, FIGO defined surgical staging criteria specifically for uterine sarcomas in order to better reflect its clinical behavior (Table 20.17).

TABLE 20.17 Surgical Staging of Uterine Sarcomas

Tumor Stage	Description
Leiomyosarcoma and Endometrial Stromal Sarcoma	
I	Tumor limited to the uterus
IA	Tumor limited to uterus, size <5 cm
IB	Tumor limited to uterus, size >5 cm
II	Tumor extends outside the uterus, but within the pelvis
IIA	Tumor extends to adnexa
IIB	Tumor extends to other pelvic tissue
III	Tumor invades abdominal tissues
IIIA	Tumor invades abdominal tissues, one site
IIIB	Tumor invades abdominal tissues, more than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	Tumor invades bladder or rectum, or has distant metastasis
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
Adenosarcoma	
I	Tumor limited to the uterus
IA	Tumor limited to endometrium/endocervix but no myometrial invasion
IB	Tumor limited to the uterus, invasion to ≤½ myometrium
IC	Tumor limited to the uterus, invasion to >½ myometrium
II	Tumor extends outside the uterus, but within the pelvis
IIA	Tumor extends to adnexa
IIB	Tumor extends to other pelvic tissue
III	Tumor invades abdominal tissues
IIIA	Tumor invades abdominal tissues, one site
IIIB	Tumor invades abdominal tissues, more than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	Tumor invades bladder or rectum, or has distant metastasis
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Treatment

Surgical excision is the only treatment of curative value. Pelvic radiation therapy has a role in local control of the tumor, but because of the propensity of uterine sarcomas for early hematogenous spread, this treatment does not affect the outcome. Leiomyosarcomas generally do not respond to radiation therapy. The combination of gemcitabine and docetaxel is standard of care for advanced or recurrent leiomyosarcoma. Cisplatin, doxorubicin, and ifosfamide have also shown activity in leiomyosarcoma as well as other uterine sarcomas. Hormonal therapy is the treatment of choice for advanced or recurrent endometrial stromal sarcomas.

Prognostic Factors

The most important prognostic factor for uterine sarcomas is tumor stage. Recurrence rates are high in general, and although stage I leiomyosarcoma has a 5-year survival rate up to 76%, diagnosis at any other stage has 5-year survival rates that are much worse (Table 20.18). Endometrial stromal sarcomas tend to be less aggressive and therefore have better survival outcomes. Sarcomatous overgrowth and deep myometrial invasion must be considered in cases of adenosarcoma because they adversely affect prognosis.

TABLE 20.18 Five-Year Survival Rates for Uterine Leiomyosarcomas, by Tumor Stage

Tumor Stage	Survival Rate (%)
I	51–76
II	25–60
III	45
IV	29

Recommended Surveillance

Physical and pelvic examinations should be performed every 3 to 6 months for 2 years after diagnosis, then every 6 months in years 3 to 5, and annually thereafter. CT imaging may also be considered for surveillance in high grade sarcomas.

Gestational Trophoblastic Disease

Incidence and Risk Factors

Gestational trophoblastic disease is characterized by an abnormal proliferation of trophoblastic tissue; all forms develop in association with pregnancy. Because this disease is associated with a gestational event, the age of occurrence spans the entire reproductive spectrum. In the United States, hydatidiform moles occur in 1 in 1,000 to 2,000 pregnancies. Among complete hydatidiform moles, approximately 20% develop malignant sequelae, including invasive moles, placental site trophoblastic tumors, and gestational choriocarcinoma. Choriocarcinoma is estimated to occur in 1 in 20,000 to 40,000 pregnancies, with half following term gestations.

A number of well-established risk factors are positively associated with hydatidiform mole. These include age younger than 20 years or older than 40 years, previous molar pregnancy (women who have had one molar pregnancy have a 0.5% to 2.5% risk of a second occurrence, and women who have had two molar pregnancies have at least a 15% to 20% risk of a third occurrence), previous spontaneous abortion (the risk increases with each subsequent spontaneous abortion), and Asian race.

Pathology

Gestational trophoblastic disease is categorized as hydatidiform mole, invasive mole, placental site trophoblastic tumor, and choriocarcinoma. Nonmetastatic disease after molar evacuation may be hydatidiform (invasive) mole or choriocarcinoma. Gestational trophoblastic disease persisting after a nonmolar pregnancy is predominantly choriocarcinoma or, rarely, placental site trophoblastic tumor. Metastatic gestational trophoblastic disease diagnosed in the early months after molar evacuation may be hydatidiform mole or choriocarcinoma. When gestational trophoblastic disease is found remote from a gestational event, it is characteristically choriocarcinoma.

Routes of Spread and Sites of Metastasis

Malignant gestational trophoblastic disease spreads primarily by hematogenous route. The most frequent site of metastasis is in the lung (80%). Other common sites are the vagina (30%), brain (10%), liver (10%), and bowel, kidney, and spleen (less than 5% each).

Clinical Features

Hydatidiform Mole. Vaginal bleeding, uterus size larger than expected for gestational age, and the presence of prominent theca lutein ovarian cysts are characteristic clinical features of hydatidiform mole. Features of partial and complete hydatidiform moles are listed in Table 20.19. Other associated findings include toxemia, hyperemesis, hyperthyroidism, and respiratory symptoms such as dyspnea and respiratory distress. Patients with partial moles may present in the same manner as those with missed or incomplete abortions: vaginal bleeding and the passage of tissue through the vagina.

TABLE **20.19** Classification of Hydatidiform Moles

Feature	Complete Mole	Partial Mole
Hydatidiform swelling of villi	Diffuse	Focal
Trophoblast	Diffuse trophoblastic hyperplasia, variable atypia	Focal trophoblastic hyperplasia, mild atypia
Embryo	Absent	Present
Villous capillaries	Absent	Many fetal red blood cells
β-hCG concentration	Usually >50,000 mIU/mL, and may be >100,000 mIU/mL	Usually <100,000 mIU/mL
Proportion that progress to choriocarcinoma	15–20%	<5%
Karyotype	46XX (majority), 46XY (less common)	Usually triploid (69XXY most common)

Clinical Feature	Incidence of Malignant Gestational Trophoblastic Disease (%)
Delayed postmolar evacuation hemorrhage	75
Theca lutein cyst >5 cm	60
Acute pulmonary insufficiency after mole evacuation	58
Uterus large for gestational dates	63
Serum β-hCG concentration >2,000 mIU/mL during 4th week postevacuation	64
Second molar gestation	40
Maternal age >40 years	25

β-hCG, beta subunit of human chorionic gonadotropin.

Pretreatment Workup for Molar Pregnancy

Careful physical examination, including pelvic examination, is required. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function, serum albumin, thyroid function tests, serum β-hCG) and chest radiography.

Malignant Gestational Trophoblastic Disease. Malignant gestational trophoblastic disease can be categorized as nonmetastatic or locally invasive, or as metastatic. Clinically, patients are often diagnosed with malignant gestational trophoblastic disease when β-hCG levels fail to normalize during monitoring following molar pregnancy evacuation.

Metastatic Workup for Malignant or Persistent Gestational Trophoblastic Disease

Metastatic workup for malignant or persistent gestational trophoblastic disease consists of the tests described for molar pregnancy plus pelvic sonography; CT scan of the chest, abdomen and pelvis; and CT or MRI of the brain. Metastatic lesions (e.g., a vaginal nodule) should not be biopsied because these lesions are very vascular and can result in significant bleeding.

TABLE 20.20 International Federation of Gynecology and Obstetrics Staging of Gestational Trophoblastic Disease

Tumor Stage	Description
I	Tumor confined to the uterine corpus
II	Metastasis to the pelvis and vagina
III	Metastasis to the lung
IV	Distant metastasis to the brain, liver, kidneys, or gastrointestinal tract

Staging

The FIGO staging schema of gestational trophoblastic disease is outlined in Table 20.20.

Treatment

Molar Pregnancy. Suction dilation and curettage is the standard treatment for molar pregnancy and is followed by close monitoring of the β-hCG antigen titer. Hysterectomy may be performed if fertility is not an issue.

Nonmetastatic Gestational Trophoblastic Disease (FIGO Stage I) . If preserving fertility is not a consideration, a total hysterectomy can be offered. If preserving fertility is desirable, adjuvant single-agent chemotherapy with methotrexate or dactinomycin is the most common treatment choice. Chemotherapy should be continued until at least one menstrual cycle beyond normalization of the β-hCG antigen titer. If there is disease resistance (i.e., the β-hCG antigen titer increases or plateaus), the patient should be treated with an alternate single agent. If resistance persists, combination chemotherapy with EMA-CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine) should be administered.

Metastatic Gestational Trophoblastic Disease (FIGO Stages II to IV): Low-Risk Disease (World Health Organization Risk Score 0 to 6) . For initial treatment, patients generally receive single-agent therapy with methotrexate or dactinomycin. If there is disease resistance, the patient should be treated with an alternate single agent. If resistance persists, combination chemotherapy with EMA-CO should be administered. If there is resistance to EMA-CO, salvage therapy includes the combination of cisplatin, bleomycin, and etoposide, or the use of EMA-EP (etoposide, methotrexate, dactinomycin alternating with etoposide and cisplatin). Combinations with paclitaxel or ifosfamide have also shown some efficacy.

High-Risk Disease (World Health Organization Risk Score 7 or Higher) . Combination chemotherapy is the treatment of choice. EMA-CO is the initial chemotherapeutic regimen, and EMA-EP or bleomycin, cisplatin, and etoposide regimens can be used as salvage treatment.

Special Considerations . Patients with brain metastases may be treated with radiotherapy for local control and prophylaxis against hemorrhage. Patients with residual solitary liver or lung lesions may be candidates for surgical resection.

Prognostic Factors

Factors that may affect a patient's prognosis and response to treatment are outlined in Table 20.21. The cure rate for low-risk gestational trophoblastic disease is essentially 100%. The cure rates for high-risk metastatic disease are still 80% to 90% with appropriate treatment.

TABLE **20.21** Prognostic Indicators for Patients with Gestational Trophoblastic Disease, by World Health Organization Prognostic Index Score

Prognostic Indicator	World Health Organization Prognostic Index Score			
	0	1	2	4
Age (years)	<40	≥40		
Type of antecedent pregnancy	Hydatidiform mole	Abortion	Term	—
Interval between antecedent pregnancy and start of chemotherapy (months)	<4	4–6	7–12	>12
β-hCG concentration (mIU/mL)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Diameter of largest tumor (cm)	<3	≥3, <5	≥5	—
Site of metastasis	Lung, vagina, pelvis	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1–4	5–8	>8
Prior chemotherapy			1 drug	≥2 drugs

β-hCG, beta subunit of human chorionic gonadotropin.
Low risk 0–6, high risk ≥7.

Recommended Surveillance

Surveillance is essentially the same for all cases of gestational trophoblastic disease, except for patients with stage IV disease, who require a longer period of surveillance. β-hCG antigen titers are measured weekly until the level is normal for 3 consecutive weeks and then measured monthly until the level is normal for 12 consecutive months. Patients with stage IV disease are typically followed for 12 to 24 months after normalization of β-hCG antigen titer values. Contraception is mandatory throughout the follow-up period.

Management of Incidental Uterine Masses Found at Laparotomy

The finding of an enlarged or abnormal uterus at the time of exploratory laparotomy or surgery for an unrelated condition can pose a therapeutic dilemma to the surgeon. Uterine fibroids, which are benign tumors of the uterus, are the most common cause of uterine enlargement. In most cases,

immediate surgical intervention is unnecessary. Unless the situation is life-threatening, hysterectomy and bilateral salpingo-oophorectomy should be performed only after proper informed consent has been obtained, especially in women of childbearing age.

Laparoscopy for the Management of Endometrial Cancer

The use of minimally invasive surgery in the staging of endometrial cancers is now the preferred surgical approach. With this approach, a thorough inspection of the peritoneal cavity, peritoneal washings (only if required by study protocols), and appropriate staging biopsies are still important. Laparoscopy has been compared with laparotomy for comprehensive surgical staging of endometrial cancer in multiple prospective trials, and has been found to be not only feasible and safe, but also associated with fewer complications and shorter hospital stays.

CERVICAL CANCER

Incidence and Risk Factors

Approximately 500,000 women worldwide develop cervical cancer each year. It is the most common cause of cancer-related death among women in underdeveloped countries. In the United States, an estimated 13,000 new cases of cervical cancer and 4,000 deaths due to this disease occur annually.

Cervical cancer is a sexually transmitted disease. It was the first solid tumor to be linked to the human papillomavirus (HPV), specifically types 16 and 18, is associated with the development of this disease. Other risk factors include early age at first intercourse, multiple sexual partners, multiparity, smoking, and other behaviors associated with exposure to the HPV. Half of women with newly diagnosed invasive cervical cancer have not had adequate cervical cancer screening, and approximately 40% of newly diagnosed women have never had a Pap smear.

Pathology

Approximately 75% of cervical cancers are squamous cell carcinomas, and 25% are adenocarcinomas, including the less common adenosquamous subtype. Rare histologic subtypes include small cell tumors, sarcomas, lymphomas, and melanomas.

Routes of Spread and Sites of Metastasis

Cervical cancer spreads through various mechanisms. It can directly invade surrounding structures, including the parametria, the uterine corpus, and the vagina. Lymphatic spread commonly occurs in an orderly and predictable sequence involving the parametrial, pelvic, iliac, and finally para-aortic lymph nodes. Hematogenous metastases and intraperitoneal implantation can also occur.

Clinical Features

Symptoms. Discharge and abnormal bleeding, including postcoital, intermenstrual, menorrhagia, and postmenopausal bleeding are often the first signs of cervical cancer. Frequent voiding and pain on urination can also occur and may indicate advanced disease.

Physical Findings . Findings on examination vary depending on the site of the lesion (endocervix or ectocervix). Careful inspection and palpation, including bimanual and rectovaginal examinations, are required to determine the size and extent of the lesion.

Pretreatment Workup

Careful physical examination must be performed, including pelvic examination and biopsy of the lesion. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function), and chest radiography.

Cervical cancer is staged by the results of the clinical examination. Therefore, unlike endometrial and ovarian cancer, staging is performed before treatment planning and not at the time of surgery. The following studies should be performed for patients with stage IB2 to stage IV cervical cancer: cystoscopy, proctoscopy, intravenous pyelography (or CT of the abdomen or pelvis), and chest x-ray or CT. MRI may also be useful, especially in distinguishing endometrial and endocervical lesions.

TABLE **20.22** Clinical Staging of Cervical Cancer

Tumor Stage	Description
I	Lesions generally confined to the cervix; uterine involvement is disregarded
IA	Preclinical cervical cancers diagnosed by microscopic analysis alone
IA1	Stromal invasion ≤3 mm deep and ≤7 mm wide
IA2	Stromal invasion >3 mm but ≤5 mm deep and ≤7 mm wide
IB	Lesions larger than stage IA lesions, regardless of whether seen clinically, or any gross lesions regardless of depth of invasion
IB1	Clinical lesions ≤4 cm
IB2	Clinical lesions >4 cm
II	Extension beyond the cervix but not to the pelvic sidewall or the lower third of the vagina
IIA1	Involvement of the upper two-thirds of the vagina, without parametrial invasion, ≤4 cm in greatest dimension
IIA2	Involvement of the upper two-thirds of the vagina, without parametrial invasion, >4 cm in greatest dimension
IIB	With parametrial involvement
III	Extension to the pelvic wall with no cancer-free space between the tumor and the pelvic wall; tumor involving the lower third of the vagina; hydronephrosis or nonfunctioning kidney unless secondary to an unrelated cause
IIIA	Involvement of the lower third of the vagina; no extension to the pelvic sidewall
IIIB	Extension to the pelvic wall, hydronephrosis, or nonfunctioning kidney
IV	Extension beyond the true pelvis or clinical involvement of the mucosa of the bladder or rectum
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Staging

The clinical staging scheme for cervical cancer is outlined in Table 20.22. The term microinvasive cervical cancer is sometimes used interchangeably with stage IA lesions. This diagnosis must be made from a cone biopsy or hysterectomy specimen.

Treatment

Stage IA1. Lesions that qualify as microinvasive disease may be treated conservatively with simple hysterectomy, or cervical conization in cases where patients desire future fertility.

Stage IA2 . Lesions that have >3 mm of invasion, standard of care

options include radical surgery with lymph node dissection or radiation therapy. Although radical hysterectomy was previously considered to be the standard of care, radical trachelectomy is considered an acceptable alternative for women who desire future fertility. Several prospective trials are currently underway evaluating the use of cervical conization with lymph node evaluation in place of radical surgery. Sentinel lymph node biopsy has been used as an alternative to pelvic lymph node dissection in cervical cancer, but further validation studies are currently ongoing.

Stages IB and IIA . Surgery or chemosensitizing radiation therapy results in similar cure rates when patients are carefully selected. The standard surgical option for patients with tumors <4 cm is radical hysterectomy with pelvic lymph node dissection, but radical trachelectomy can be used in patients desiring future fertility. Sentinel lymph node biopsy is also being used by some surgeons in the place of lymph node dissection. Nonsurgical management may include weekly chemotherapy and 45-Gy external-beam irradiation followed by brachytherapy. Among patients who undergo surgery, chemoradiation is used postoperatively in those believed to be at high risk for disease recurrence.

Stages IIB to IVA . Chemosensitizing radiation therapy is the treatment of choice for locally advanced disease. Surgery may be used as adjuvant therapy for patients with persistent central disease after radiation therapy.

Stage IVB . Stage IVB disease is treated primarily with chemotherapy because the disease is disseminated. Chemotherapy regimens containing a platinum agent are most common, but regimens which include the combination of topotecan and paclitaxel can also be used. Bevacizumab has now been approved in combination with other regimens in this setting. Other biologic agents and immunotherapy are currently under investigation. Radiation therapy may be considered for local control and palliation of symptoms.

Recurrent Disease

Treatment of recurrent cervical cancer depends on the location of the disease and the type of primary treatment the patient received. Central recurrence may be managed with pelvic radiation therapy in patients treated with primary surgery alone. Pelvic exenteration can be considered in patients who have undergone prior radiation therapy. Patients who have

unresectable disease or distant metastatic disease are treated with systemic chemotherapy. Chemotherapy options are similar to those used in metastatic disease.

Prognostic Factors

The most important prognostic factors for stage I disease include lymphovascular space involvement, tumor size, depth of invasion, and presence of lymph node metastases (Table 20.23). For patients with stage II to IV disease, tumor stage, presence of lymph node metastases, tumor volume, age, and the patient's performance status are key prognostic factors. The survival rates for patients with cervical cancer are shown in Table 20.24. Among patients who have recurrent cervical cancer, 75% of patients are diagnosed with their recurrent disease within 2 years, and 95% within 5 years.

TABLE 20.23 Incidence of Cervical Cancer Lymph Node Metastasis (Surgically or Based on Imaging), by Tumor Stage

	Incidence (%) as Indicated by Lymph Node Metastasis	
Tumor Stage	**Pelvic**	**Para-Aortic**
I		
IA1	<1	<1
IA2	2–9	<1
IB	12–51	2–9
II		
IIA	27–50	11–21
IIB	39–54	10–21
III	50–68	11–25
IV	55–85	27–60

TABLE 20.24 Five-Year Survival Rates for Patients with Cervical Cancer, by Tumor Stage and Histologic Subtype

Tumor Stage and Histologic Subtype	Survival Rate (%)
Stage I	
Squamous	69–93
Adenocarcinoma	68–84
Stage II	
Squamous	55–58
Adenocarcinoma	46
Stage III	
Squamous	31–34
Adenocarcinoma	20–30
Stage IV	
Squamous	6–17
Adenocarcinoma	8–9

Recommended Surveillance

Physical and pelvic examinations should be performed every 3 to 6 months in the first 2 years after diagnosis depending on risk factors, every 6 to 12 months in years 3 to 5 depending on risk, and annually thereafter. A Pap smear should also be obtained annually, and imaging should only be used if a recurrence is suspected.

VULVAR CANCER

Incidence and Risk Factors

Vulvar cancer accounts for 3% to 5% of gynecologic malignancies. Almost 6,000 new cases are diagnosed annually in the United States. The incidence of vulvar cancer tends to be bimodally distributed. Most cases are solitary lesions that occur in postmenopausal women, and the tumors are often associated with chronic vulvar dystrophy. Recently, a subset of tumors has been identified in a younger population; these tumors tend to be multifocal and are associated with HPV infection.

The cause of vulvar cancer appears to be multifactorial. Risk factors include HPV infection, advanced age, low socioeconomic status, hypertension, diabetes mellitus, prior lower genital tract malignancy (e.g., cervical cancer), and immunosuppression.

Pathology

Eighty percent of vulvar malignancies are squamous cell carcinomas, and up to 10% are malignant melanomas. Less common histologic subtypes

include basal cell carcinomas, Bartholin gland carcinomas, Paget disease, and adenocarcinomas arising from sweat glands.

Routes of Spread and Sites of Metastasis

Vulvar cancer spreads by direct extension to the vagina, urethra, and rectum. Embolization to regional lymphatics (e.g., the groin) and hematogenous spread to distant sites can also occur.

Clinical Features

Symptoms. Chronic pruritus, ulceration, and nodules on the vulva are the most common presenting symptoms of this disease.

Physical Findings . Lesions may arise from the labia majora (30% to 50%), labia minora (20% to 30%), periclitoral area (10% to 20%), and perineum or posterior fourchette (10% to 15%). Multifocal lesions occur less frequently. Lesions may appear as a dominant mass, warty area, ulcerated area, or thickened white epithelium.

Diagnosis

Any suspicious area must undergo biopsy. A Keyes punch biopsy should be used, and lidocaine without epinephrine should be administered for anesthesia.

Pretreatment Workup

Careful physical examination, including pelvic examination and measurement of the lesion, is required. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, liver function), and chest radiography CT or MRI should be performed if indicated. PET/CT should be considered in patients with invasive melanoma.

Staging

In 2009, FIGO updated vulvar staging criteria to better reflect the clinical and prognostic factors related to this disease (Table 20.25).

Treatment

Stage I. Wide local excision should be performed if the lesion has less than 1 mm of invasion into the underlying tissue. Wide radical excision

with a traditional 2-cm gross margin (measured with a ruler) and lymph node evaluation of the ipsilateral groin are appropriate for all other stage I lesions. Bilateral groin evaluation should be performed if the lesion is within 2 cm of the midline. Although in the past superficial groin dissections were used for lymph node evaluation, several prospective randomized trials have found sentinel lymph node evaluation to have excellent sensitivity and decreased morbidity. Sentinel lymph node biopsy is now used routinely in patients with a single tumor measuring less than 4 cm in diameter, with groin dissection performed in cases where sentinel lymph nodes are not detected. Adjuvant radiation therapy may be administered for higher-risk patients.

TABLE 20.25 Surgical Staging of Vulvar Cancer

I	Tumor confined to the vulva
IA	Lesion ≤2 cm in size and stromal invasion ≤1 mm; negative nodes
IB	Lesion >2 cm in size and stromal invasion >1 mm; negative nodes
II	Tumor of any size with adjacent extension (lower 1/3 urethra, lower 1/3 vagina, anus); negative lymph nodes
III	Tumor of any size with or without adjacent extension, with positive inguinofemoral lymph nodes
IIIA1	1 lymph node metastasis ≥5 mm
IIIA2	1–2 lymph node metastasis(es) <5 mm
IIIB1	2 or more lymph nodes metastases ≥5 mm
IIIB2	3 or more lymph node metastases <5 mm
IIIC	Positive node(s) with extracapsular spread
IV	Tumor invades other regional or distant structures
IVA1	Invasion of other regional structures (upper 2/3 urethra, upper 2/3 vagina), bladder mucosa, rectal mucosa, or fixed to pelvic bone
IVA2	Fixed or ulcerated inguinofemoral lymph nodes
IVB	Any distant metastasis, including to the pelvic lymph nodes

Stage II . Wide radical excision and resection of bilateral inguinal nodes is the standard approach to stage II disease. The local recurrence rate is similar when the more conservative approach of radical wide excision is used instead of radical vulvectomy. Adjuvant radiation therapy may be indicated if high-risk features are present, including tumor-free margin of resection less than 8 mm, tumor thickness greater than 5 mm, or lymphovascular space invasion.

Stage III . Treatment must be individualized for each patient with stage III disease. Options include surgery, radiation, and a combination of treatment modalities. A modified radical vulvectomy (or a radical wide local excision) with inguinal and femoral node dissection can be performed; pelvic and groin radiation therapy should be administered if positive groin nodes are found. Preoperative radiation therapy (with or without radiation-sensitizing chemotherapy) can be given to increase the operability of the lesion and decrease the extent of resection. Radical excision with bilateral superficial and deep groin node dissection can then be performed. Radiation therapy alone is an option if the patient is ineligible for radical surgery or the lesion appears to be inoperable based on location near vital structures.

Stage IV . Treatment of stage IV disease must also be individualized. Options include radical vulvectomy with pelvic exenteration, radical vulvectomy followed by radiation therapy, preoperative radiation therapy (with or without radiation-sensitizing chemotherapy) followed by radical surgical excision, and radiation therapy (with or without radiation-sensitizing chemotherapy) and/or systemic chemotherapy if the patient is ineligible for surgery or the patient has distant metastatic disease.

Recurrent Disease

Treatment of recurrent disease depends on the site and extent of the recurrence. Options include radical wide excision with or without radiation therapy (depending on prior treatment and extent of recurrence), groin node debulking followed by radiation therapy (depending on prior treatment), systemic chemotherapy, and pelvic exenteration. Regional or distant metastasis are difficult to treat, and palliative therapy is often the only option.

Prognostic Factors

The prognostic factors for vulvar carcinoma are various. Inguinal node metastasis appears to be the single most important prognostic variable. Other factors include lymphovascular space invasion, tumor stage (Table 20.26), lesion size, lesion site, histologic grade, and depth of invasion.

Recommended Surveillance

Physical and pelvic examinations should be performed every 3 to 6 months

in the first 2 years after diagnosis depending on risk factors, every 6 to 12 months in years 3 to 5 depending on risk, and annually thereafter. A Pap smear should be obtained according to current guidelines if the patient still has a cervix, and imaging should only be used if a recurrence is suspected.

TABLE 20.26 Five-Year Survival Rates for Patients with Vulvar Cancer, by Tumor Stage

Tumor Stage	Survival Rate (%)
I	79–97
II	59–64
III	43–49
IV	13–24

VAGINAL CANCER

Incidence and Risk Factors

Primary vaginal cancer represents 1% to 2% of malignancies of the female genital tract. The average age at diagnosis is between 65 and 70 years. Most vaginal neoplasms represent metastases from another primary source.

Risk factors associated with vaginal cancer include history of HPV infection, chronic vaginal irritation, prior abnormal Pap smear result with cervical intraepithelial neoplasia, prior hysterectomy (59% of patients with primary vaginal cancer), prior treatment for cervical cancer, and in utero exposure to diethylstilbestrol during the first half of pregnancy. Diethylstilbestrol was used from 1940 to 1971 to prevent pregnancy complications such as threatened abortion and prematurity. Clear cell carcinoma of the vagina developed in approximately 1 in 1,000 women exposed to diethylstilbestrol in utero. Since this agent is no longer available, the incidence of this disease has dramatically declined.

Pathology

Approximately 80% to 90% of vaginal cancers are squamous cell neoplasms. Other histologic subtypes include adenocarcinoma (10%), sarcoma, melanoma, and clear cell carcinoma.

Routes of Spread and Sites of Metastasis

Vaginal cancer metastasizes via direct extension to adjacent structures. It can also spread through a well-established lymphatic drainage distribution. Lesions of the upper two-thirds of the vagina metastasize directly to pelvic lymph nodes, and lesions of the lower third of the vagina metastasize primarily to the inguinofemoral nodes and secondarily to pelvic nodes. Hematogenous spread is likely a late occurrence because, in most cases, the disease is confined primarily to the pelvis.

Clinical Features

Symptoms. Painless vaginal bleeding and vaginal discharge are the primary symptoms associated with vaginal cancer. Bladder symptoms, tenesmus, and pelvic pain, which are usually indicative of locally advanced disease, are less commonly seen.

Physical Findings . Lesions are located primarily in the upper third of the vagina, usually on the posterior wall. The appearance of lesions varies. Surface ulceration is usually not present, except in advanced cases. Visualization of lesions identified by Pap smear may require colposcopy.

Pretreatment Workup

Careful physical examination, including pelvic examination with colposcopy, is required unless the lesion is visible. Other components of the pretreatment workup include clinical tests (e.g., complete blood cell count, serum glucose, blood urea nitrogen, creatinine, and liver function), chest radiography and cystoscopy or proctoscopy, depending on the site and extent of the lesion. CT or MRI should be performed to determine the extent of the disease.

Staging

The clinical staging scheme for vaginal cancers is outlined in Table 20.27.

Treatment

Stage 0. Stage 0 disease may be treated by surgical excision, laser ablation, and, in some cases, topical 5-fluorouracil or imiquimod.

TABLE

Clinical Staging of Vaginal Cancer

20.27

Tumor Stage	Description
0	Carcinoma in situ, intraepithelial carcinoma
I	Tumor limited to the vaginal wall
II	Tumor involving subvaginal tissue but not extending to the pelvic wall
III	Extension to the pelvic wall
IV	Extension beyond the true pelvis, or involvement of the bladder or rectal mucosa
IVA	Spread to adjacent organs and/or direct extension beyond the pelvis
IVB	Any distant metastasis

Stage I . All stage I lesions (including lesions of the upper vaginal fornices) may be treated with radiation therapy, usually using a combination of external beam and intracavitary or interstitial brachytherapy. Lesions of the upper vaginal fornices may be treated with radical hysterectomy and lymphadenectomy or with radiation therapy alone.

Stages II to IV . External-beam radiation therapy and intracavitary or interstitial radiation therapy are used for stage II to stage IV disease. Concurrent radiosensitizing chemotherapy is often considered in the form of weekly cisplatin. Radiation to the groin lymph nodes may be indicated as well.

Recurrent Disease

Treatment of recurrent vaginal cancer depends on the extent and location of the recurrence. Options include wide local excision, partial vaginectomy, and pelvic exenteration. Chemotherapy may be given for distant metastatic disease; however, the efficacy of chemotherapy is not well known.

Prognostic Factors

The most important prognostic factor for vaginal cancer is the tumor stage (Table 20.28).

Recommended Surveillance

Physical and pelvic examinations should be performed every 3 to 6 months in the first 2 years after diagnosis depending on risk factors, every 6 to 12

months in years 3 to 5 depending on risk, and annually thereafter. A Pap smear should also be obtained annually, and imaging should only be used if a recurrence is suspected.

TABLE 20.28 Five-Year Survival Rates for Patients with Vaginal Cancer, by Tumor Stage

Tumor Stage	Survival Rate (%)
I	78–84
II	52–75
III/IV	36–58

Recommended Readings

Epithelial Ovarian Cancer

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21 Neurosurgical Malignancies: Treating Tumors of Brain and Spine and Their Effects on the Nervous System

Ian E. McCutcheon

The interplay of neurosurgery with other disciplines in the broader field of surgical oncology leads to frequent instances of neurosurgical treatment in patients whose tumors originated outside the central nervous system. Tumors also originate within the brain or spine and require neurosurgical care. To many oncologists the nervous system remains an arcane, poorly understood area yet it is one with profound implications on patient outcome. Neurosurgical oncologists aim to cure or palliate tumors when possible, but even more so to preserve function at the highest possible level and for the longest period of time. It is a technically demanding discipline very much concerned with maintaining the functions that make life worthwhile. This chapter will provide an overview of fundamental clinical scenarios and basic tumor types relevant to the practice of neurosurgical oncology in a cancer center.

CLINICAL EVALUATION

Neurologic Examination

All encounters with patients suspected of harboring some form of neurologic disease must perforce begin with an interview and neurologic examination. All too often this portion of the physical examination is skipped or notated scantily or not at all in the chart, yet a good history and intelligently focused neurologic examination will yield 90% of the elements needed to make clinical decisions for a tumor affecting the neuraxis. Ultimately the interpretation of such information depends on a sound working knowledge of the anatomy of the nervous system. The 10 subsystems (cerebral cortex, pyramidal tracts, basal ganglia, brainstem, cranial nerves, cerebellum, spinal cord, nerve roots, peripheral nerve, and

muscle) each cause different changes on neurologic examination that allow accuracy in anatomical localization.

Questions to Ask

First, *is the patient conscious?* The classic way of measuring consciousness is by grading eye movements, verbalization, and motor function on the Glasgow Coma Scale (GCS), in which perfect wakefulness and function result in a score of 15 and complete coma without even reflex movements yields a score of 3 (Table 21.1). Note that even a dead person has a score of 3, and prognosis is very poor in a living patient with this low a GCS. The scale measures whether such responses occur spontaneously or only after varying degrees of stimulation. Even patients in deep coma will preserve flexor or (in the worst case) extensor motor responses to such deep painful stimuli as a sternal rub. In the relatively awake patient, speech function can be assessed by noting speech patterns during conversation, but subtle patterns of dysphasia may elude the observer unless he or she addresses pointed questions to the patient. In most patients the speech areas reside in the brain's left hemisphere. However, because speech function arises in the *right* hemisphere in 15% of left-handed subjects, this generalization is not absolute. Depending on which part of the speech network is affected by a lesion, patients can show difficulties with expressing words (Broca's area), with naming objects (uncinate fasciculus), with reading (posterior parasylvian), or with understanding spoken phrases (Wernicke's area). In addition speech may be impaired from a motor perspective if the cranial nerves subserving coordination of tongue, throat muscles, and vocal cords are impaired.

TABLE 21.1 Glasgow Coma Scale

		Score
Eye opening	Spontaneously	4
	To speech	3
	To pain	2
	None	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Motor response	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

Is the patient weakened or paralyzed in one or more limbs? Even in a comatose patient, differential degrees of withdrawal to painful stimuli can uncover a weakness. In the awake patient, a simple request to pull or push against resistance provided by the examiner, and made for each of the four limbs, can uncover various patterns of weakness. These include a hemiparesis (weakness of one side of the body), quadriparesis (weakness in all four limbs and implying a lesion of the cervical spinal cord or brain), or paraparesis (weakness of both legs, implying a spinal lesion above the lumbosacral junction). In an oncology patient the possibility of tumor affecting neural elements at the appropriate location in the nervous system must be considered before other diagnoses common in the nononcologic population (e.g., stroke, trauma, etc.).

Does the patient have a myelopathy? This term implies a disorder of the spinal cord as opposed to the brain, and ruling myelopathy in or out is done in any patient who complains of sensory or motor symptoms that could have arisen from such a spinal lesion. The delicacy of the spinal cord in the face of extrinsic (or for that matter, intrinsic) compression means that such compression cannot be allowed to persist for long before permanent deficits ensue. Myelopathy is detected by examining: (1) reflexes at the knees and elbow (quadriceps and biceps reflexes, respectively), (2) muscle tone, and (3) response of the toes to plantar stimulation, that is, the Babinski response. When myelopathy is present, reflexes and tone are increased and the plantar response is extensor.

Can the patient see? Four of the 12 cranial nerves are used for seeing

(optic nerve, cranial nerve II), eye movement (cranial nerves III, IV, and VI), or eyelid opening (cranial nerve III). Eye movements should be checked because they give an indicator of the function of the brainstem, where the nuclei of these cranial nerves reside, and because increases in intracranial pressure (ICP) can affect ocular motility most commonly by causing a sixth nerve palsy in which lateral movement (abduction) of one or both eyes is impaired. In addition, increases in ICP can cause papilledema visible on fundoscopy. Perfect vision requires the integrity of a system that extends from the retina through the optic nerves, chiasm, and tracts back through the geniculate body of the thalamus, and thence through the optic radiations to the calcarine cortex in the occipital lobes. If the patient passes a good visual examination then malfunction of a significant portion of the brain has been excluded.

Can the patient swallow? This aspect of the neurologic examination is often overlooked, but the ability to swallow is critically important to good outcome for any patient undergoing surgery for a tumor. Patients with impairment of the gag reflex or with pharyngeal dysmotility are harder to wean safely off ventilatory assistance, are more prone to aspiration and its consequences, and often cannot achieve oral intake sufficient to maintain the good nutrition needed for postsurgical healing. Decisions about gastrostomy or about transnasal tube feeding should be made early in patients in whom such issues have been discovered.

Finally, *can the patient walk?* Walking is a complex function that needs inputs from sensory systems, proprioceptive processing systems, and motor systems to prevent falls. Tumors in the cerebellum, which acts as a computer processing and modulating proprioceptive inputs and motor outputs, cause ataxia. Intrinsic disease within nerves (e.g., diabetic neuropathy) can reduce sensory input and cause a patient to stumble more easily. When seeing a patient with a recent history of stumbling or falling, the surgical oncologist should examine for signs of incipient myelopathy indicating an impending spinal cord compression. As the window of opportunity in such cases is small (24 hours from loss of ambulation), a decline in the ability to walk can be a vitally important clue, and demands prompt investigation.

INCREASED INTRACRANIAL PRESSURE

Basic Principles

The cranium in man is a rigid structure. Its contents include the brain, blood (arterial and venous), and cerebrospinal fluid (CSF). Because intracranial volume is constant, when an intracranial mass is introduced compensation first occurs through a reciprocal decrease in the volume of venous blood and CSF. This concept, known as the Monro–Kellie doctrine, is most applicable in adults. Children younger than the age of skull suture fusion will show cranial expansion only when high ICP is chronic. CSF volume increases with age due to brain atrophy.

When compensatory mechanisms have been exhausted, minute changes in volume produce precipitous increases in pressure. The pressure–volume curve reflects very small increases in pressure when an expanding mass begins in the intracranial compartment. ICP rises more precipitously as compensation allowed by egress of CSF and venous blood disappears. When ICP overcomes arterial pressure, perfusion ceases and brain death occurs.

The blood–brain barrier (BBB) is formed by linked astrocytic foot processes along the adventitial surfaces of cerebral endothelial cells. It prevents many substances carried in the blood from reaching the brain, and protects neural tissue from potentially toxic materials. It also regulates the flow of biologically active molecules into the brain. Lipid-soluble substances can usually penetrate more effectively than amino acids and sugars, which are transported across the endothelium by specific carrier-mediated mechanisms. When the barrier is disrupted, plasma components cross into the brain and cause vasogenic edema. Relative disruption of the BBB by intracranial tumors causes local edema around the tumor leading to neurologic malfunction in the edematous zone. In addition, the BBB prevents most chemotherapy agents from penetrating into the brain and has stymied the development of effective medical treatments for brain tumors. In the past 35 years only four drugs have been approved by the FDA for brain tumor therapy: *bis-chloronitrosourea (BCNU)*, now little used, but which has the advantage of lipid solubility; its cognate alkylating agent *CCNU*, which is given orally; *temozolomide*, also given by mouth and having a low side-effect profile; and *Avastin*, an anti-angiogenic monoclonal antibody whose efficacy in extending survival is controversial. Polycarbonate wafer impregnated with BCNU (Gliadel®) has been separately approved for treatment of glioblastoma and is placed during surgery along the walls of the surgical resection cavity. It provides a modest increase in survival through slow diffusion of the drug locally into

potential sites of microscopic invasion in an edematous peritumoral brain.

Cerebral edema is treated with steroids (usually dexamethasone) and in more refractory cases with osmotic agents such as mannitol, urea, or hypertonic saline. Use of steroids is routine after resection of intracranial or spinal tumors as a way of reducing the flare-up of edema commonly seen after intraoperative tumor manipulation. Tumors that produce copious amounts of vascular endothelial growth factor (VEGF) give the most extensive edema; a classic example is metastasis from renal cell carcinoma.

Cerebral blood flow is determined most significantly by the cerebral perfusion pressure (CPP), defined as the difference between the incoming mean arterial pressure (MAP) and the opposing ICP. The formula is:

$$\text{CPP} = \text{MAP} - \text{ICP} = \text{diastolic pressure} + [1/3\ (\text{pulse pressure})] - \text{ICP}$$

As ICP rises, CPP decreases. Under physiologic conditions several factors regulate cerebral blood flow: systemic blood pressure, pCO_2 and pH in the arterial blood, and pO_2. Autoregulation maintains blood flow to the brain at a constant level over a wide range of MAP. When MAP is low, cerebral arterioles dilate to allow adequate flow. Increased systemic blood pressure causes arterioles to constrict for the same purpose. At MAP <50 mm Hg perfusion is inadequate; with MAP >150 the autoregulatory system fails and cerebral blood flow increases, leading to vasogenic edema and hypertensive encephalopathy.

Arterial pCO_2 is the most potent stimulus for dilation of cerebral arterioles. As pCO_2 decreases from 80 to 15 mm Hg, cerebral blood flow decreases. Since it diminishes cerebral blood flow and blood volume, hyperventilation can be used to treat increased ICP. A patient with decreased level of consciousness (GCS ≤9) from increased ICP is typically intubated for airway protection and prevention of aspiration, but also for hyperventilation to a pCO_2 of 28 mm Hg. Such patients are maintained normoxic or slightly hyperoxic. As hypoxia causes cerebral arteriolar dilation, maintaining good oxygenation helps dampen increases in ICP.

The normal ICP is 10 to 15 mm Hg (13 to 20 cm H_2O) in an awake patient. Causes of raised ICP are given in Table 21.2. Increased ICP harms the brain in two ways. First, ischemia can occur when CPP reaches critically low levels and can lead to stroke. Second, focal masses (e.g., tumors or hematomas) cause distortion of the brain which if profound

enough causes compression of brainstem structures vital to life. Herniation of the cerebellar tonsils through the foramen magnum, or the midbrain and aqueduct of Sylvius through the tentorial incisura, further elevate ICP by blocking CSF pathways. Increases in ICP are better tolerated when shift of brain structures is absent. When ICP is increased slowly and chronically by generalized syndromes such as pseudotumor cerebri (a little-understood condition labeled variously as a disorder of CSF absorption), a structural defect in venous sinuses, or a product of morbid obesity, neurologic dysfunction may be absent or limited to specific cranial neuropathies.

TABLE 21.2 Common Causes of Increased Intracranial Pressure (ICP)

Pathologic Process	Examples
Localized masses	Hematomas: epidural, subdural, intracerebral
	Neoplasms: gliomas, meningiomas, metastases
	Abscesses
	Focal edema: from trauma, infarction, tumor
Obstruction of CSF pathway	Obstructive hydrocephalus
	Communicating hydrocephalus
Obstruction of major venous sinus	Depressed skull fracture over sinus
	Thrombosis from dehydration or oral contraceptive use
Diffuse brain edema	Encephalitis, meningitis
	Diffuse head injury
	Subarachnoid hemorrhage
	Water intoxication
	Lead poisoning causing encephalopathy
Idiopathic	Pseudotumor cerebri

Herniation occurs when the brain moves within the cranial cavity relative to the edge of dural folds intended to prevent its movement. The four main types of brain herniation are:

1. *Cingulate herniation*, in which pressure is greater in one hemisphere than the other, leading to shift of the cingulate gyrus beneath the falx.
2. *Uncal herniation*, which is the most clinically dramatic and most common herniation syndrome. It occurs when a lesion in the middle cranial fossa (temporal lobe) expands the uncus, the most inferomedial structure of the temporal lobe, and displaces it against

the peduncle of the midbrain. Uncal herniation gives a clinical syndrome of progressively impaired consciousness, dilation of the ipsilateral pupil ("blown pupil"), and contralateral hemiplegia. Disturbance of consciousness comes from disturbance of the reticular activating system in the midbrain, pupillary dilation from compression of the oculomotor nerve and its parasympathetic pupillary constrictors, and hemiplegia from the compression of the corticospinal tract above its decussation.

3. *Central transtentorial herniation,* which is caused by hemispheric lesions in the frontal or parietal areas of the brain. Here the diencephalon and midbrain shift down through the tentorial incisura. The clinical syndrome is more difficult to recognize than that of uncal herniation and may include small reactive pupils, obtundation, loss of vertical gaze, and Cheyne–Stokes respiration.
4. *Tonsillar herniation* is caused by expansion of a posterior fossa mass. The cerebellar tonsils move through the foramen magnum into the upper spinal canal and compress the dorsolateral medulla and upper cervical cord. This leads to hypertension, cardiorespiratory impairment, neurogenic hyperventilation, and impaired swallowing and consciousness. Ultimately death occurs due to cardiac and respiratory instability.

Symptoms of increased ICP include headache, worse in the early morning due to a rise of pCO_2 from hypoventilation during sleep and increased venous pressure from the recumbent position. However, headache is not a specific symptom and it is perfectly possible to have increased ICP without headache. The combination of headache and vomiting is suggestive, and accompanying neurologic signs like papilledema and cranial neuropathies are further confirmatory. The speed of onset of the increase in ICP influences symptoms as well. More chronic or slowly progressive rises in pressure are less likely to cause obtundation or pronounced neurologic decline.

Monitoring ICP

Continuous monitoring of ICP is important in patients whose neurologic examination and radiologic examinations support the suspicion of increased pressure. Controlling such pressure rises significantly reduces morbidity and mortality in neurosurgical patients. Although the most common indicators for such monitoring are closed head injury and

subarachnoid hemorrhage, patients in the oncology setting may require it in a number of circumstances including after posterior fossa surgery (to determine whether pre-existing hydrocephalus has cleared); when brain injury has led to coma and thus abrogated use of the neurologic examination as an index of brain function; or when an intracranial hemorrhage caused by chemotherapy-induced thrombocytopenia leaves the patient at risk for hydrocephalus or further bleeding, with decisions about shunting or clot evacuation assisted by ICP measurement over time.

The most effective method of measuring ICP is through placement of a ventriculostomy drainage catheter. This is inserted through a frontal burr hole made either at the bedside or in the operating room. The catheter is tunneled a short distance to prevent infection, and exits the scalp through a separate stab incision. It is connected to a pressure transducer and a drainage system. The catheter can be used to measure pressure but also to drain CSF to treat ICP increases when it exceeds a prespecified limit. This limit is set by raising or lowering the loop of the drain, which provides resistance to CSF egress. For example, when the loop is set at 10 cm above the external auditory meatus (the typical "zero" point), no drainage occurs unless CSF pressure exceeds 10 cm of H_2O.

Treatment of Increased ICP

The first order of business in ICP treatment is always to address the cause directly. If the increased pressure results from the presence of an intracranial mass such as a tumor or clot, the mass should be promptly removed. Such surgery restores ICP to normal more effectively than any other measure. However, the clinical situation is often complex with other causes of increased ICP at play such as hydrocephalus or cerebral edema. The main methods for ICP control (other than direct surgery) are:

1. *Ventricular drainage*. This can be maintained for 10 to 14 days before catheter change is recommended to reduce the risk of ventriculitis or meningitis. Antibiotic-coated catheters are now standard and keep the rate of infection low.
2. *Mannitol*. The usual dose is 0.25 g/kg IV q4–6h. It is given in small boluses, and an increase in serum osmolality of as little as 10 moSm/mL can be enough to reduce cerebral edema significantly. Mannitol also improves perfusion by reducing blood viscosity. It is effective for 48 to 72 hours, but its use is not recommended beyond that time frame.

3. *Hypertonic saline*. This has been used increasingly in the past 10 years, and studies have shown that it is as effective as mannitol.
4. *Hyperventilation*. This requires intubation, and in a patient above the level of coma it also requires paralysis and sedation. Hyperventilation should be moderate with end-tidal pCO_2 lowered to 28 to 32 mm Hg. Reducing pCO_2 below that level will compromise cerebral blood flow and compound the ischemia already produced by increased ICP.
5. *Loop diuretics* (furosemide; Lasix®). These are sometimes used as an adjunct to mannitol, but are not dependable when used alone for the reduction of ICP.
6. *Steroids*. Dexamethasone is given at a loading dose of 10 mg IV followed by 4 to 8 mg q6h. It should be tapered over 7 to 10 days once its therapeutic effect has been achieved. Other steroids (hydrocortisone or methylprednisolone) are not used, as they are insufficiently potent or have inconsistent metabolism that impairs their effectiveness.
7. *Barbiturate coma*. Short-acting barbiturates to induce coma are a last resort in managing increased ICP. These agents reduce cerebral metabolism and cerebral blood flow; the most commonly used is thiopental (loading dose, 3 to 10 mg/kg IV over 10 minutes; maintenance dose, 1 to 2 mg/kg/hr). Serum levels are checked and should be maintained at 3 to 4 mg/L. Patients in barbiturate coma need intensive monitoring and may require vasopressors to counteract arterial hypotension. Spectral EEG monitoring confirms burst suppression.

SEIZURES

Seizures in the tumor patient are caused by cortical irritation provoked by brain tumor (either primary or metastatic), intracranial bleeding (usually subdural), electrolyte abnormality (in sodium, calcium, or magnesium), infections like meningitis or encephalitis, or head trauma after a fall. As they are most easily corrected, metabolic causes should always be eliminated, but radiologic investigation is usually needed as well. Seizures should be controlled because they are distressing to the patient and his or her family, but also because the hypermetabolic effects of active epilepsy can impair function in an already compromised brain around a tumor, or in a zone of cerebral edema. Seizures can be focal or general, simple or complex, and occur with or without loss of contact with surroundings. A

patient with a chronic seizure disorder need not be scanned every time a new seizure is noted. However, a patient with no history of seizures should undergo scanning by computed tomography (CT) or magnetic resonance imaging (MRI) to examine the brain for bleeding, edema, or increased ICP needing intervention. The seizure itself can usually be suppressed by levetiracetam (Keppra) or the older drugs, phenytoin (Dilantin) or valproic acid (Depakote). Occasionally seizures will be refractory and will require more than one drug or in cases of status epilepticus, intubation, and intravenous barbiturates. The most common cause of new-onset seizure in a previously healthy adult is not tumor but stroke. Nevertheless, brain tumors yield seizures as a presenting symptom in 20% to 30% of cases. After surgery, the seizure tendency does not decrease for ≥2 weeks after an offending mass lesion has been resected. If a patient has had seizures prior to surgery and is on anticonvulsants to control them, we continue the drug therapy for 3 to 6 months after surgery before attempting a taper in those who have been seizure-free. After an uncomplicated craniotomy without prior history of seizure, we do not routinely use anticonvulsants after surgery. For those with complicated cases involving significant brain trauma in epileptogenic zones like the temporal lobe or motor cortex, anticonvulsant prophylaxis after surgery is used by surgeon preference.

MYELOPATHY

Myelopathy refers to the clinical syndrome caused by dysfunction of the spinal cord, but does not specify where in the spinal cord such dysfunction has arisen. Syndromes differ depending on the spinal level, as lesions in the cervical cord can produce weakness and sensory loss in all four limbs, whereas lumbar lesions produce such loss only in the legs because of their location well below the exit point of the nerves supplying the arms. The spinal cord also influences bladder and bowel function and in the neck gives rise to the phrenic nerve (C3–5) controlling diaphragmatic excursion. The most common reason for myelopathy in an oncology practice is extrinsic compression of the spinal cord by a metastatic tumor within a vertebral body or pedicle immediately adjacent to the cord. Such patients commonly present with an ascending sensory loss that begins in the feet and can ascend no higher than the level of the lesion itself. In addition, they often show weakness more likely affecting the legs and impairing the ability to walk. They also can complain of bladder and sometimes bowel incontinence. The key to successful treatment of a compressive

myelopathy is early intervention before loss of the ability to walk. A patient who has been bed-bound for more than 24 hours is unlikely to benefit from a decompressive operation. Indeed, the first symptom is often not a neurologic dysfunction at all, but back pain caused by compression of nerve roots or by local instability due to bony collapse or ligamentous disruption. Any patient with a history of cancer who presents with back pain should have an MRI of the symptomatic spinal region to rule out spinal involvement by tumor. Certainly an aging population can contain patients with cancer who also have coincident degenerative disease of the spine with spondylosis, disc protrusion, and osteophyte formation causing a typical degenerative pain syndrome. However, it is never wise to assume the absence of neoplasm in a patient with a history of systemic cancer, and MRI will also help in diagnosing nontumor pathologies.

RADIOLOGIC ASSESSMENT

Imaging for tumors of the brain and spine has evolved significantly during the past 20 years and now depends heavily on computerized scans of various types to diagnose lesions, select which are appropriate for surgery, and provide data helpful in planning operative strategies.

Computed Tomography

Computed tomography (CT) is a vital component of oncologic diagnosis for sites in the chest, abdomen, and pelvis. However, its utility in diagnosing brain lesions has diminished somewhat with the advent of the more anatomically detailed images provided by MRI. When oncologists suspect intracranial tumor they often order CT almost by reflex, but MRI will generally be needed whether the CT finding is positive or negative. As the cost differential is not great, the exposure to ionizing radiation is eliminated, and the sensitivity is greater, we recommend using MRI rather than CT as the first-line scanning modality for patients being screened for intracranial or spinal tumor. The advantages of MRI include the anatomical detail that it provides, the multiplanar capacity that permits three-dimensional visualization, the sensitive depiction of the extent of edema, and the ability of MRI to show subtle lesions through the hypersensitive FLAIR sequence usually included in such scans.

CT remains useful in limited areas. First, it is much quicker to obtain than an MRI, thus should be used for any patient in whom urgent imaging

is needed. In a postoperative patient in whom concern has arisen over the possibility of a clot in the resection cavity, CT is typically requested. Second, the scanner is more open and allows easier access to an unstable patient than the closed tube of an MRI, so CT is favored for very sick patients in the ICU for whom constant nursing access is necessary. Third, the depiction of bone is better on CT than MRI, thus a tumor of the skull vault or skull base usually requires a CT as part of the radiologic workup. It can also be used to detect calcification in tumor as a way of narrowing the differential diagnosis. Examples of this include meningiomas and craniopharyngiomas, both benign tumors that often calcify. Fourth, CT angiography has supplanted digital subtraction angiography as a mode of screening for intracranial aneurysm or other vascular malformations. Formal angiography is still required for patients with vascular lesions who require surgical or endovascular intervention, but CT angiography is an excellent way of deciding whether a patient with an intracerebral hematoma of the temporal lobe and a history of cancer has an aneurysm or a metastatic tumor as the inciting cause of the bleed. Finally, some patients with pacemakers may not be able to undergo MRI safely and thus a CT may be required.

In the spine, depiction of bony anatomy can be done with great precision by CT using reconstructed sagittal and coronal, as well as axial views. Three-dimensional reconstruction of the spine in patients with complex bony defects, particularly those who have had prior surgery, can be a very valuable tool in planning further surgery.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the most useful radiographic modality in neurosurgical oncology. Frequently used sequences for imaging tumors of the brain include T1-weighted spin-echo before and after injection of gadolinium contrast agent; T2-weighted spin-echo or fast-spin echo sequences; and FLAIR images. Fat suppression can be used as needed to enhance image clarity. Standard depiction of tumors occurs on T1 pre- and postcontrast sequences, with T2 sequences useful for showing edema, cyst, or tumor water content. FLAIR sequences bring out subtle abnormalities than can be missed on other less sensitive images. In addition, diffusion weighted images show areas of diminished perfusion indicative of stroke, and diffusion tensor imaging can be used for mapping fiber tracts such as the corticospinal tract or uncinate fasciculus, the

localization of which can enhance safety during surgery. Functional MRI is now commonly used for patients in whom preoperative mapping of speech areas is desirable. Such patients include those with a tumor near Broca's or Wernicke's area, or the left-handed patient in whom localization of speech to the left hemisphere is not guaranteed. Motor mapping can also be done on functional imaging, but is less often requested because intraoperative methods of motor mapping are easy to apply and highly accurate.

MRI spectroscopy has been advocated as a method of distinguishing one tumor type from another by virtue of the varied metabolic spectra produced by tumors *in vivo*. This is a controversial area, and we do not routinely use spectroscopy for that purpose. Its main utility is in distinguishing tumor from posttreatment effect in patients who have undergone prior radiotherapy or chemotherapy. Even in that group, however, the sensitivity and specificity are imperfect and biopsy may be needed to make that distinction. The classic tumor signature is an increase in the choline/creatinine ratio (and decrease in *N*-acetyl aspartate) over that of normal brain.

In the larger world of oncology, combining CT with positron emission tomography (PET) is commonly done for metastatic surveys. This is not particularly helpful for brain imaging because of the diffuse hypermetabolism exhibited by the brain on such images. However, they can detect metastatic deposits in the spine and pinpoint areas that should undergo MRI for anatomic delineation. In addition, such imaging is quite useful in assessing tumors of peripheral nerve as it can depict formerly benign tumors undergoing dedifferentiation to neurofibrosarcoma, an absolute indication for surgical resection.

PRIMARY TUMORS OF CENTRAL NERVOUS SYSTEM

Brain

Primary brain tumors arise in most cases from neuroglial cells, and fall into an umbrella category, the gliomas. These make up 50% to 65% of intracranial tumors in most series. Their pathology, locations, and prognosis are diverse. Annually in the United States 20,000 new cases of malignant primary brain tumors are detected, and gliomas form >90% of these. The median age at diagnosis is the mid- to late 50s, but such tumors can occur in childhood and the incidence of the most malignant form

(glioblastoma) increases in the elderly. Rare familial syndromes have been identified, for example, the Li–Fraumeni and Turcot syndromes, which link gliomas with other nonneural cancers, but most are sporadic and lack specific risk factors. Basic types are listed in Table 21.3.

Histologic Classification

Since the initial attempts at histologic classification of gliomas by Cushing and others in the 1920s and 1930s, the multiplicity of definitions has muddied the literature tremendously. Both three- and four-tiered systems have been suggested, but the current WHO classification contains four grades for astrocytomas. Grade I lesions, which includes the subependymal giant cell astrocytomas and pilocytic astrocytomas, are uncommonly seen; grade II lesions are the classical "low-grade" astrocytomas. The uniformly invasive group of anaplastic astrocytomas (grade III) represent the first level of malignancy, and glioblastomas and gliosarcomas are classified in grade IV. With the current and growing emphasis on genomic analysis, several molecular alterations can be used as distinguishing characteristics beyond the traditional grading schemes that rely on histology alone. Most notably, the mutation status of the *IDH1* gene predicts survival better than traditional grading systems based on histology.

TABLE 21.3 Familial Syndromes Predisposing to Gliomagenesis

	Gene	Chromosome	CNS Tumor	CNS Tumor Risk	Tumors Outside CNS	Systemic Tumor Risk
Li–Fraumeni syndrome	*TP53*	17p13.1	Astrocytoma Medulloblastoma Choroid plexus carcinoma	14%	Breast carcinoma Adrenal cortical carcinoma Soft tissue sarcoma	Men: 70%/Women: 100%
Neurofibromatosis type 1	*NF1*	17q11.2	Pilocytic astrocytoma Astrocytoma	10% 1%	Neurofibroma Malignant peripheral nerve sheath tumor Gastrointestinal stromal tumor Pheochromocytoma Leukemia	>97% 10% 15% 4% Rare
Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	*PTCH1 SUFU*	9q22.3 10q24.3	Medulloblastoma	<2% (PTCH1) 30–40% (SUFU)		
Turcot syndrome type 1	*MLH1* *MSH2* *PMS2* *MSH6*	3p21.3 2p21 7p22.2 2p16	Astrocytoma	53%	Colorectal carcinoma Hematologic cancers	100%
Turcot syndrome type 2	*APC*	5q31	Medulloblastoma	<1%	Familial adenomatous polyposis	100%
Tuberous sclerosis	*TSC1 TSC2*	9p34 16p13.3	Subependymal giant cell astrocytoma	10–15%	Hamartomas (skin, retina, heart, lung, kidney)	>90%

Astrocytic Tumors

Pilocytic Astrocytomas . These WHO grade I tumors commonly affect patients in the second decade of life and do not invade adjacent brain tissue, nor do they usually undergo malignant degeneration. The majority (two-thirds) occur in the cerebellum, 30% in the optic nerves, chiasm, and hypothalamus, and the rest in the cerebral hemispheres. The treatment for these is surgery which if complete is generally curative. Although some have advocated using radiotherapy and chemotherapy at recurrence, this methodology is controversial and reoperation is often advocated in that circumstance. Such tumors in the cerebellum or cerebral hemisphere are typically resectable with minor or no morbidity. However, those termed "optic gliomas," typically seen in patients with neurofibromatosis type 1 (NF1), are much less amenable to surgery without compromise of vision. Typically such patients are observed and followed conservatively, and treated with radiotherapy should they progress.

Astrocytomas . The low-grade (grade II) astrocytomas make up 10% to 25% of gliomas in most series and are usually detected in the fourth or fifth decade. Such tumors grow slowly and often present with seizures or are incidentally found. They do not show well on CT in many cases, and MRI is a more reliable modality for comparative imaging over time. Traditionally these tumors have been managed conservatively, but in the past decade a growing consensus has arisen in the literature over the desirability of resection prior to malignant transformation. The mean time from detection to such transformation is 8 years, at which point they become much more aggressive and have a significant likelihood of killing the patient. Because mitosis is so sparse in such tumors, chemotherapy and radiotherapy each have not been particularly effective in controlling them long term. However, a study by Buckner et al. (2016) showed that patients receiving both modalities survive longer than do those receiving radiotherapy alone; debate continues over which chemotherapy is most appropriate in this population. Patients with such tumors may be reluctant to undergo surgical resection because of their lack of symptoms, but we do advocate early removal to as complete a degree as possible given local functional anatomy. Enhancing completeness of resection in these relatively subtle lesions is facilitated greatly by intraoperative MRI (Fig. 21.1). We achieve a significant improvement in radiographically complete resection with such technology relative to historical controls, and a concomitant increase in survival.

Anaplastic Astrocytoma . These tumors occur in a slightly older age group (fifth or sixth decades of life) either de novo or as a result of malignant degeneration within a low-grade astrocytoma. They form 10% to 15% of the gliomas and commonly present in the cerebral hemispheres with seizures and focal neurologic deficits. These tumors, unlike the low-grade tumors, frequently show contrast enhancement on MRI and have more surrounding edema, mass effect, and rapidity of growth. Age and preoperative functional status are prognostic, but the goal of treatment is not to cure but to extend life and maintain function. Current standard treatment consists of surgical resection followed by radiotherapy and then chemotherapy with temozolomide. A variety of chemotherapy regimens have been tried in the past, but most have been unsuccessful in prolonging life by more than a few months. Most of these tumors will recur eventually as glioblastomas. The median survival is 3 years with about 20% surviving 5 years.

Glioblastoma . This is the most common intrinsic brain tumor and forms half of gliomas in most series. It usually occurs in the sixth or seventh decade, but can arise at any age. The common location is the cerebral hemisphere with occasional tumors in the corpus callosum giving rise to the classic “butterfly glioma” pattern that extends into both hemispheres from its central point of origin. Personality change and headache are common, but seizures are only sometimes seen. Glioblastoma is much less common in the posterior fossa and very rare in the spinal cord.

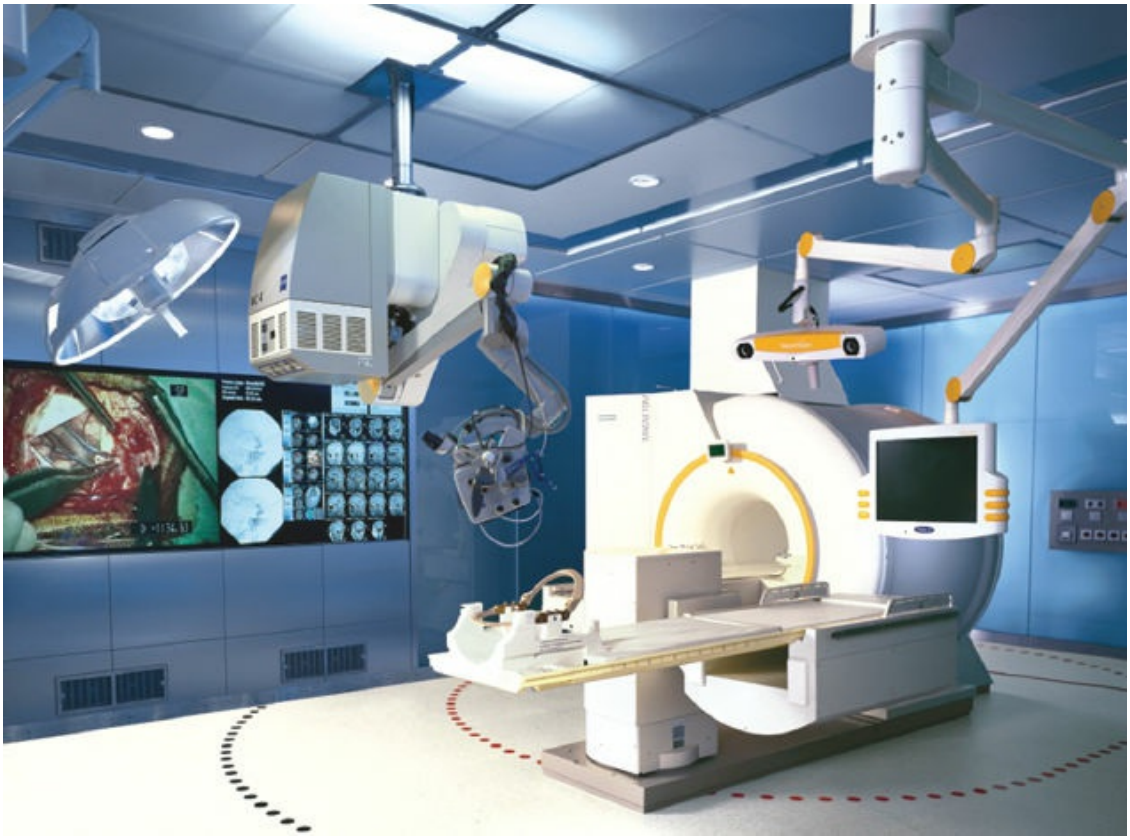

Figure 21.1 The intraoperative MRI is located within a magnetically shielded room with integrated components allowing efficiency of workflow. The patient lies on a bed outside the 5-Gauss line for surgery, then is covered to maintain sterility and rotated into the MRI scanner for imaging at intervals during the operation.

Such tumors have a heterogeneous pattern of enhancement with typically a centrally necrotic area that is relatively hypointense on MRI (Fig. 21.2). The edges are indistinct and such tumors may cross the midline. They have significant perilesional edema in many instances. The histology is characterized by vascular proliferation, frequent mitotic figures, hypercellularity, and necrosis, which is the hallmark of these tumors.

Glioblastomas are the most aggressive brain tumors. Their treatment should be aggressive as well, and include a meaningful attempt at radical surgical resection followed by whole-brain radiotherapy and chemotherapy in patients able to tolerate it. Lacroix et al. showed at MDACC that the greatest positive influence on survival occurs after resection of ≥98% of the contrast-enhancing portion of the lesion. However, increasing benefit was seen at all percentages of resection above 90%. Thus, if resection is to

be done, it makes little sense to remove less than 90% of these tumors, and the ideal approach is complete radiographic removal. Since these tumors have an infiltrating edge and have been shown through biopsy of theoretically unaffected brain to have infiltrating cells as far as 4 cm from the radiographic edge of the tumor, the “gross total” resection is by no means total. For this reason, adjunctive therapies must be used and must be to make a more meaningful impact on this disease. In the realm of chemotherapy, the most studied drugs are the nitrosoureas (BCNU and its analog CCNU) which give a 10% increase in 18-month survival and little change in median survival. With temozolomide and newer multi-drug combinations, the median survival in our institution is 21 months. This is significantly better than the 9 to 12 months of survival quoted in most textbooks, but still far too short for the patient struck by this tumor in the peak of life, as many are.

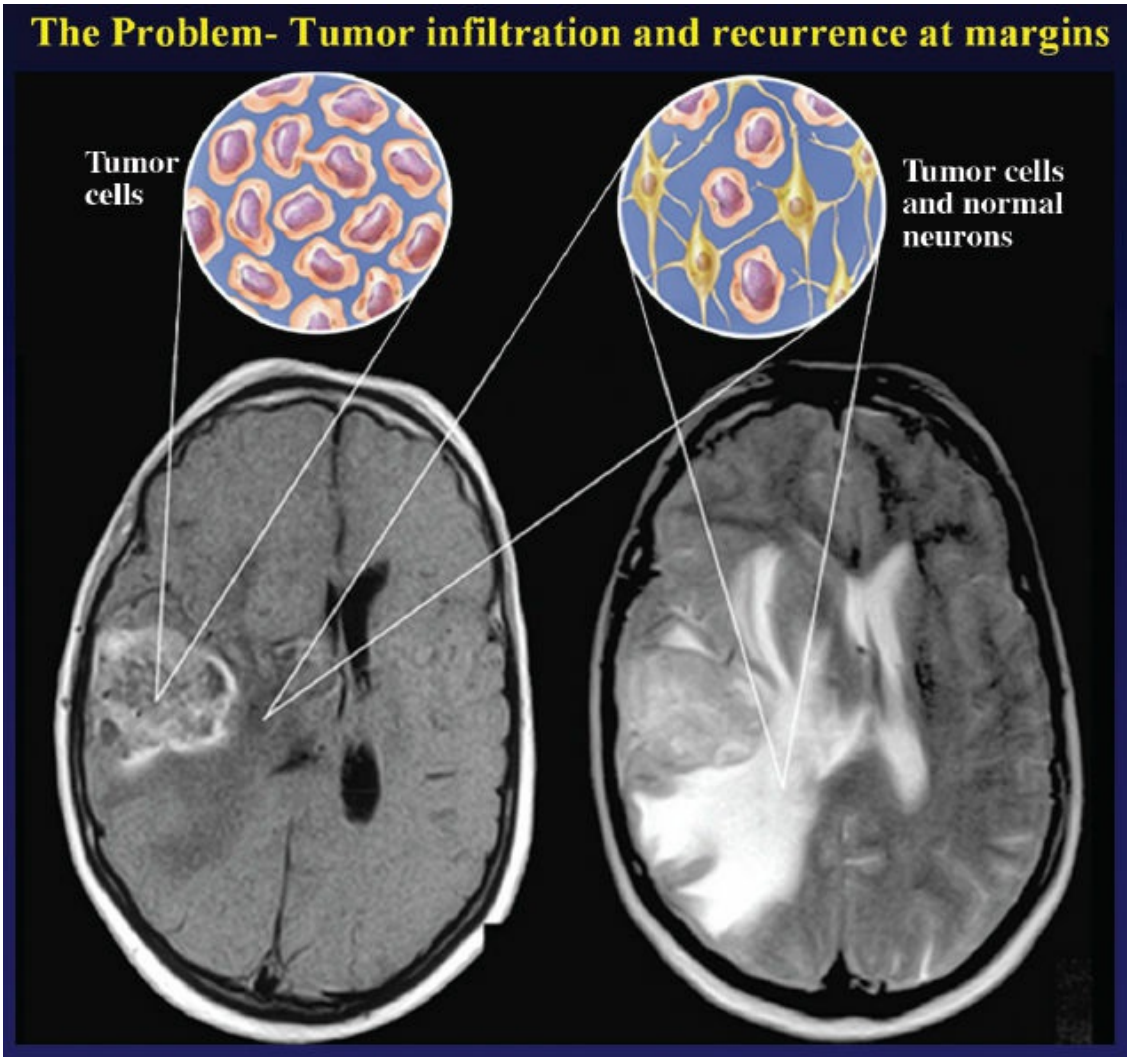

Figure 21.2 MRI of patient with glioblastoma in the right

hemisphere. Postcontrast T1-weighted image is on the left side of the panel, and T2-weighted image shows edema on the right. Even when gross total removal of contrast-enhancing portions is achieved, the margins remain with infiltrating tumor cells that cannot be controlled by surgery.

Innovative approaches include biologically based therapies such as immunotherapy and gene therapy. In immunotherapy, tumors positive for the EGF receptor variant III (35% to 40% of glioblastomas) showed significant prolongation of survival to 30 months after which all recurred through the growth of clones not expressing that epitope. A study using the Delta 24 oncolytic virus given through intraparenchymal injection of the tumor or the edges of its resection cavity is underway at MDACC, and has shown some clinical efficacy. Kunwar et al. used convection-enhanced delivery to infuse IL-13-PE38QQR (IL-13 linked to pseudomonas exotoxin) into the brain's interstitial space in patients with glioblastoma, but without significant added benefit. Given that this approach combined a new mode of delivery with a new therapeutic agent, it is hard to tell whether the agent would be effective if delivered by other means, or whether the mode of delivery would work with a differently targeted agent.

The 5-year survival for glioblastoma is <5% and recurrence occurs within 2 to 3 cm of the original resection margin in 80% of patients. The remaining patients also show recurrence, but farther afield within the brain, and even in the opposite hemisphere. Metastasis to extraneural sites is vanishingly rare. Occasional patients are seen with gliomatosis, that is, a multifocal involvement of more than one lobe of the brain. Because many patients with systemic cancer are elderly, and glioblastoma tends to be a disease of older patients, it is not infrequent to find a glioblastoma arising in a patient being treated for a second cancer, so it is important for general oncologists to recognize its manifestations, implications, and modes of therapy.

Oligodendrogliomas

These tumors form 10% to 15% of gliomas and typically involve the cerebral hemispheres, with involvement of the thalamus and brainstem much less likely. They present in the fifth or sixth decade, frequently with seizures although headache and focal deficit may also occur. They are more likely to be calcified than are the astrocytomas, indicative of their

slower pace of growth. The majority present as grade II lesions, but the occasional anaplastic tumor arises de novo as a grade III lesion. The classic histologic finding is a perinuclear halo known as a “fried egg” appearance which is caused by shrinkage of the cellular components during exposure to formalin. Mixed oligoastrocytomas are possible and are defined by staining with glial fibrillary acid protein (GFAP), an astrocytic marker not present in oligodendroglioma.

Cairncross et al. have shown that chromosomal analysis further differentiates a subgroup of oligodendrogliomas forming 60% to 70% of the whole, with deletions of chromosome 1p, 19q, or both. Those tumors with such deletions are more sensitive to chemotherapy (prototypically, procarbazine, CCNU, and vincristine), radiotherapy, or both. Median survival is affected by the presence or absence of these chromosomal alterations: it is 3 to 5 years for patients with tumors without loss of heterozygosity, and 10 to 12 years for those with loss of heterozygosity. Therapy for oligodendrogliomas mirrors that for astrocytomas, with surgery followed by radiotherapy and chemotherapy used in most cases. Chemotherapy is overall more effective in oligodendrogliomas than astrocytomas. However, recent work shows a survival difference within the glioblastoma population based on patients’ mutational status in the *IDH1* gene. Such molecular analyses will be increasingly important in personalizing therapeutic choices of drugs most likely to work in tumors most likely to respond.

Metastatic Brain Tumors

Between 20% and 40% of patients with systemic cancer develop brain metastasis. Such tumors can be extra-axial (involving the dura and subdural space, or leptomeninges and subarachnoid space), but usually occur within the brain parenchyma. MRI confirms that two-thirds of such patients have more than one metastasis in the brain, and that the classic solitary metastasis is uncommon. As with other tumor types, available methods for treating brain metastases include surgery, focused or diffuse irradiation, or chemotherapy.

The true incidence of brain metastasis is unknown. CT under-represents the number of metastases in many patients and is insufficiently sensitive to use as a screening study. MRI is the imaging modality of choice as it can show not only subtle lesions but also leptomeningeal disease, the presence of which greatly impacts prognosis and mode of treatment. Brain

metastases are the most common intracranial tumors in adults. Their incidence has risen because of increased detection by MRI and because of longer survival from more effective systemic therapies. The biology and thus the nuances of surgical treatment differ among the various histologies, so brain metastasis cannot be considered as a single disease. Only 1% to 2% of ovarian and prostate cancers spread to the brain, but at least half of melanomas do so, when other systemic metastases are present. The most common histologic type of brain metastasis is carcinoma of the lung (40% to 60% of large clinical series), followed by those derived from breast cancers (15% to 20%) and melanoma (10% to 20%). Colorectal and renal cell carcinomas account for 5% to 10% each. These five sources yield most cerebral metastases. Melanoma has the highest propensity to spread to the brain but is less represented than lung cancer because of the much greater incidence of the latter in the general population. In children with systemic cancer, the incidence of intracerebral metastasis is <5% and arises mainly from neuroblastoma, Wilms tumor, and sarcoma (especially rhabdomyosarcoma).

Two-thirds of patients with brain metastasis present with neurologic decline, usually focal deficits or impairment of cognitive function. Many asymptomatic patients actually have disordered cognition unrecognized by external observers. Increase in ICP through edema or blockage of CSF pathways can combine with local ischemia to give localized cerebral dysfunction. In 20% to 30% of patients seizures occur, more often in those with multiple metastases. Two histologies are particularly prone to intratumoral bleeding: melanoma and choriocarcinoma in which the bleeding rates are 45% and 95%, respectively. On MRI a large amount of edema around a recent hematoma (<6 hours old) suggests but does not confirm a tumor beneath the hematoma. Metastases can produce cysts, especially carcinomas of the breast and adenocarcinomas of the lung, but other histologies can also provoke them.

Radiology

MRI is the most sensitive test, and thus should be used for surveillance even when it is contraindicated. Most metastases are hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images. Hemorrhage may be suggested by the presence of a hemosiderin ring hypointense on T2 along the tumor margin, or by hyperintensity on precontrast T1-weighted images. Some small tumors may fail to enhance

due to relative preservation of the BBB, but can still be detected on FLAIR sequences.

These tumors are classically located at the junction between gray and white matter. However, they can grow anywhere in the brain. As radiologic diagnosis is sometimes inexact, presumed metastases meeting the above criteria may turn out to be other tumor types when resected. Patchell et al. (1990) reported that 11% of patients thought to have a single brain metastasis actually had other pathology. Multiple brain lesions in patients without a history of cancer represent metastasis in only 15% of cases. Spinal tap is the only other diagnostic test sometimes helpful in workup of such patients, and can unmask the occasional case of cysticercosis misdiagnosed as metastasis. If cytologic analysis is positive for malignant cells in CSF, the patient has leptomeningeal dissemination of tumor and may benefit from intrathecal instillation of chemotherapy. This is usually done through an Ommaya reservoir, a silastic chamber placed beneath the scalp in the frontal area with a ventriculostomy tube leading into the frontal horn of the lateral ventricle. As the ventricles are the site of origin for CSF, this places the drug at the beginning point of the pathways of CSF flow, which are thus able to carry it widely through the subarachnoid space.

Life expectancy of patients with brain metastasis depends more on the status of their systemic disease than the status of their brain metastasis (which can usually be controlled); however, patients with leptomeningeal dissemination of tumor have the worst prognosis with a median survival of 3 months. They are at risk for hydrocephalus and survival can be prolonged by shunting, but their prognosis remains poor even with aggressive multimodality therapy including intrathecal chemotherapy and radiotherapy.

Unknown Primary Tumors

One-third of patients with symptomatic brain metastases have no systemic cancer previously diagnosed. Such patients should undergo metastatic workup to screen the most likely primary sites (lung, breast, kidney, colon, and skin). Lung cancer is the culprit in 70% of these patients. Thus, chest x-ray, mammography (in women), and a skin survey should be obtained. CT of the chest, abdomen, and pelvis, or PET-CT, should also be done. In the absence of any accessible extracranial tumor, stereotactic biopsy or (more often) open resection of the cerebral tumor should be done to

confirm diagnosis prior to treatment. The source of an unknown primary brain metastasis remains occult in 15% of patients despite extensive investigation.

Treatment

The management of brain metastasis is both complex and controversial. It includes surgery, stereotactic radiotherapy, whole-brain radiotherapy, and chemotherapy. Patients with edema on MRI receive steroids to suppress it. Clinical improvement is generally noted within 12 hours of beginning steroid therapy in 70% to 80% of cases, but the peak effect may be delayed for up to a week. After surgery a steroid taper is instituted over 1 to 2 weeks. We reserve anticonvulsants for patients with a known seizure history.

Single Brain Metastasis

The median survival for patients without treatment is 6 weeks. Adding steroids improves this to 3 months, and external beam (whole-brain) radiotherapy improves survival to 4 to 6 months. Randomized clinical trials comparing surgery + radiotherapy with radiotherapy alone suggest a significant benefit from surgery on overall survival and quality of life (Table 21.4). If systemic disease is not controlled, however, the benefits of controlling brain metastasis are eroded.

The variables to be considered when selecting patients with a single metastasis for surgery are: (1) the overall clinical status, (2) the surgical accessibility of the tumor, (3) its size, and (4) its radiosensitivity. Only patients with absent or controlled systemic disease and no leptomeningeal dissemination of tumor derive significant benefit from the removal of brain metastasis. Obviously distinguishing “controlled” from “uncontrolled” systemic disease can be somewhat arbitrary. We usually look for expected survival of ≥4 months in patients being considered for surgery, while advanced age, poor medical condition, and KPS <70 argue against surgery.

Ultimately brain metastasis is a multifocal or even a diffuse process. Focal treatments like surgery or radiosurgery can suppress the disease, but eliminating it may require whole-brain irradiation to treat microscopic foci unseen on MRI as well as small tumor fragments left at sites of resection. However, standard radiotherapy is less effective than radiosurgery for radiographically evident tumors because the dose must be lowered to prevent toxicity to normal brain. Standard whole-brain radiotherapy uses

10 fractions of 3 Gy each for a total dose of 30 Gy. Radiosurgery applies a single fraction of 15 to 18 Gy with highly conformal dosimetry at each target site.

TABLE 21.4 Randomized Trials Comparing (Surgery + Postop Radiotherapy) Versus (Radiotherapy Alone)

	Patchell et al. (1990)	Vecht et al. (1993)	Mintz et al. (1996)
No. of patients	48	63	84
Inclusion criteria	>17 years old Single lesion KPS > 60 Lesion surgically accessible No LMD Very radiosensitive tumor excluded	>17 years old Single lesion Functional level at least 2 Life expectancy >6 months No LMD No SCLC or lymphoma	<80 years old Single lesion KPS > 40 Lesion surgically accessible No LMD No SCLC, lymphoma, or nonmelanoma skin cancer
Disseminated cancer	38%	32%	45%
Imaging	MRI	CT	CT
Histologic proof in radiotherapy group	Yes	No	Occasional
Radiotherapy regimen	36 Gy/12 fractions	40 Gy/20 fractions (b.i.d.)	30 Gy/10 fractions
Outcome (weeks)	Surgery better	Surgery better	No difference
Surgery	40	40	24
Radiotherapy	15	24	24

LMD, leptomeningeal disease; SCLC, small cell carcinoma of lung; CT, computed tomography; MRI, magnetic resonance imaging; KPS, Karnofsky performance scale.

Surgery Versus Radiosurgery: The Conundrum

The basic dilemma for most patients with brain metastasis is whether to treat with surgery or use focused methods of stereotactic irradiation to target the lesion(s) (Fig. 21.3). Attempts at randomized trials have not been wholly successful due to the difficulty of convincing patients to enroll. Many patients have a bias favoring stereotactic radiosurgery as it has the benefit of avoiding a surgical incision, anesthesia, and a hospital stay of several days with recovery over several weeks. Radiosurgery procedures are done in a single day and require little to no posttreatment recovery. They do require placement of a head frame with resulting moderate

discomfort, but most patients tolerate this well. Retrospective comparison implies a similar outcome between surgery and stereotactic irradiation but is unreliable because of selection bias. Prospective comparison has suggested that resection yields lower rates of local recurrence than does radiosurgery, but their relative effects on survival are less clear. Advantages and disadvantages of radiosurgery are shown in Table 21.5. At MDACC we now treat five patients with radiosurgery for each one treated surgically.

Drawbacks to radiosurgery remain. Even when local control of a tumor is achieved, patients with significant peritumoral edema may remain steroid-dependent for 3 months or even longer. Many tumors show temporary mild enlargement and intensification of enhancement during the first 1 to 2 months after radiosurgery. Persistence of edema, development of necrosis exerting mass effect, or frank tumor growth after radiosurgery imply treatment failure, and are all indications for resection. With both surgery and radiosurgery, local rates of control of 85% to 95% are achieved, which are similar for various histologies; and median survivals range from 8 to 13 months depending on histology. So-called "radioresistant" tumors such as melanoma, renal cell carcinoma, and soft tissue sarcomas do respond to radiosurgery because of the high doses used, but local rates of control are still lower than in carcinomas of the lung and breast.

Recent comparisons of patients operated by en bloc resection versus piecemeal removal have shown that en bloc resection yields better local control and also a lower rate of subsequent leptomeningeal dissemination. Clearly surgical technique is important in metastasis removal. Tumors that are soft and friable, necrotic, cystic, or hemorrhagic are particularly difficult to remove cleanly, and in such cases strong consideration should be given to subsequent adjuvant radiotherapy either as a stereotactic boost to the operative cavity or by whole-brain mode.

The morbidity after radiosurgery is comparable to that seen after surgery. In each the local recurrence rate is 5% to 15%. Hemorrhage and seizures can occur after either. Worsening of cerebral edema is unusual, however, after resection of a metastasis most postsurgical patients improve neurologically and can stop steroids within 1 to 2 weeks. The 30-day postoperative mortality is 2% to 3% in major centers with an overall morbidity of 10% to 15%.

We recommend surgery to patients with a single, accessible metastasis

causing marked mass effect and neurologic decline. When systemic disease is controlled the brain metastasis can usually be removed without inciting or worsening neurologic deficits, and surgery is a good option. However, locations in deep portions of the brain or in/near eloquent areas may shift the balance in favor of radiosurgery. Very large tumors respond best to surgery. Radiosurgery is the preferred treatment for tumors <3 cm in diameter, especially in patients whose age or medical condition renders them imperfect candidates for surgery or whose tumors are located in areas of relatively higher surgical risk.

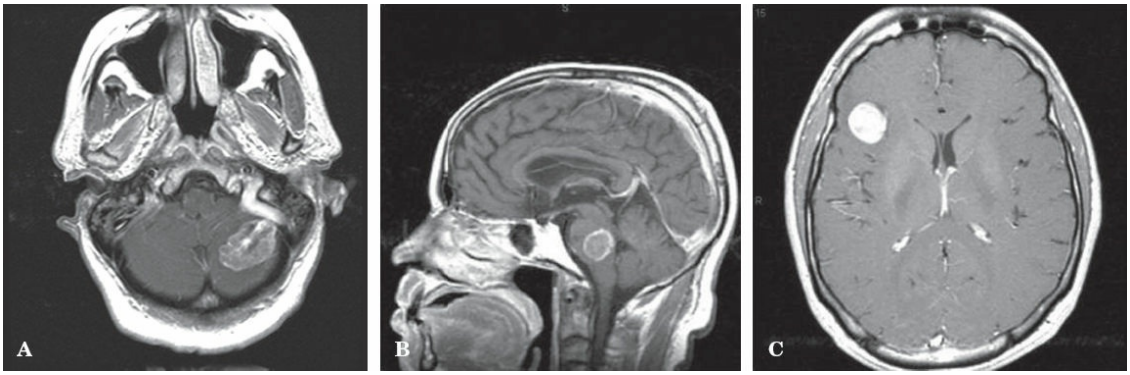

Figure 21.3 **A:** MRI showing metastasis from carcinoma of colon in left cerebellar hemisphere. This patient should have surgery, because the lesion's size puts it slightly above the 3 cm limit for stereotactic radiosurgery, and its location in the posterior fossa means that brainstem should be protected from the possibility of edema postirradiation. **B:** This metastatic carcinoma of unknown primary sits within the brainstem, a site that is unsafe for surgery. It should be treated with stereotactic radiosurgery. **C:** This small metastasis from renal cell carcinoma sits in the right frontal lobe. This area is safe for both surgery and radiosurgery, and this patient can be assigned either treatment, with little advantage to be gained from choosing one over the other.

TABLE 21.5 Advantages Versus Disadvantages of Surgery

Advantages

No incision
Treats surgically inaccessible lesions
More easily tolerated by physiologically compromised patient
Short hospital stay (usually 1 day)

Disadvantages

Poor targeting for tumors >3 cm in diameter
Tumor persists on scans, so must be followed to prove success
No tissue diagnosis
Persistent edema or radionecrosis may require surgical removal of tumor
Cannot be used on targets within 5 mm of optic nerve/chiasm/tract without significant dose modification

Patient preference is a major driving factor in making the choice between surgery and radiosurgery. The perception of radiosurgery as noninvasive often trumps the therapeutic benefits of surgery in the minds of patients and physicians alike.

Radiotherapy After Surgery

Whole-brain irradiation is often given after surgical resection of brain metastases to reduce local recurrence and eliminate occult micrometastases. The conventional dosing scheme is 30 Gy/10 fractions. Larger fraction sizes give increased risk of neurotoxicity, but this regimen does not eliminate altogether the long term cognitive effects of irradiating the entire brain. Given the longer survivals now achieved by multimodality or personalized treatment regimens for various cancers with a propensity for brain metastasis, such delayed toxicity (which usually takes ≥2 years to develop) has been seen more often recently, and is very difficult to treat.

Patchell et al. (1998) described a randomized trial assigning surgical patients to postoperative observation versus radiotherapy. The study was limited to patients with a single, completely resected brain metastasis, and the radiotherapy consisted of 50.4 Gy in 28 fractions, a significantly longer course of treatment than is given in most centers. This regimen lowered the local rate of recurrence from 46% to 10% and the appearance of brain metastasis at new sites from 37% to 14%. Differences in overall survival and functionally independent survival were not statistically significant. This study is flawed in that a local recurrence rate of 46% is higher than that expected with surgery alone, thus conclusions about the efficacy of whole-brain irradiation in controlling local recurrence are muddied. It does appear to reduce formation of new brain metastases, which suggests that

micrometastases are indeed present in many patients.

Whole-brain radiotherapy for single lesions after surgical removal (or after radiosurgery) is thus a valid treatment option. It is equally valid to withhold radiotherapy and monitor closely for recurrence, at which point focal therapy can be repeated as needed. The decision to give such radiotherapy should be based on the number of tumors visible in the brain, and on their size and radiosensitivity. Although we have traditionally favored whole-brain radiotherapy for patients with multiple tumors, we now usually treat these with stereotactic radiotherapy focused on multiple separate targets to reduce the risk of provoking cognitive deficits. When used, it works best on small tumors (<2 cm) and on those with radiosensitive histology.

Multiple Metastases

A nihilistic attitude is maintained by many neurosurgeons toward patients with multiple brain metastases. However, studies from our institution have shown through retrospective and case-control analysis that multiple surgical resections via one or more simultaneous craniotomies are both safe and effective. In the case-control study by Bindal et al., survival of patients undergoing complete resection of up to three metastases was significantly better than that of patients in whom one or more tumors was left unresected, and was similar to survival after removal of a single metastasis, without increase in morbidity or mortality. Surgery should definitely be considered for a single, dominant, surgically accessible metastatic tumor causing mass effect and neurologic compromise, regardless of the presence of smaller and less dangerous tumors elsewhere in the brain. When a cluster of tumors can be removed through a single craniotomy, this too may be beneficial in preserving neurologic function. In many large centers (including ours) local therapy (with or without subsequent whole-brain irradiation) is offered for multiple metastases in patients with controlled systemic disease, KPS >70, and life expectancy >3 to 4 months. Argument continues over the ideal cut-off number for brain metastases above which focal therapy should not be offered. In one typical clinical scenario, lesions >2.5 cm in diameter are resected and the remainder, especially those that are surgically inaccessible, are treated with radiosurgery. When all tumors are <3 cm in diameter, focal therapy should be offered for all tumors, since treating some but not others yields little benefit.

Chemotherapy

Chemotherapy has not been very successful in controlling cerebral metastases. The BBB provides a pharmacologic sanctuary for metastatic lesions. Occasional responses by chemosensitive solid tumors such as breast cancer or nonseminomatous germ cell tumors of the testis belie the sturdiness of the barrier, and 10% of melanoma brain metastases will respond to temozolomide given systemically. New targeted agents given systemically also yield imperfect control of brain metastases, but some produce dramatic shrinkage of these lesions. In general, however, chemotherapy for brain metastasis gives little improvement in survival or quality of life, and is usually a last resort after other therapies have failed.

Small Cell Carcinoma: A Special Case

Randomized prospective trials have shown that prophylactic whole-brain radiotherapy reduces the incidence of brain metastasis in patients with small cell carcinoma of the lung, a histology exquisitely sensitive to irradiation. Enthusiasm for this technique is tempered by concern over its effects on cognitive function in patients who survive longer than a year. In addition, radiation necrosis can occur idiosyncratically beyond 9 months from radiation delivery. Neurologic toxicity can be limited by keeping fractions small and by withholding concurrent chemotherapy. The current consensus holds that prophylactic whole-brain irradiation confers a survival advantage of 5% at 3 years and a reduction in the incidence of brain metastasis by 25%, and is thus considered standard treatment for patients with this disease who are in complete remission after initial treatment. The situation for patients who have not achieved complete remission is less clear.

Surgical Technique for Brain Metastasis

Ideally resection is done en bloc when removal of a circumferential 5-mm margin of brain is not limited by nearby functional areas. When it is so limited, or when tumors are friable or cystic, a careful piecemeal technique must be used. When intratumoral hemorrhage eliminates the en bloc option, the blood should be carefully drained from the tumor pocket and not allowed to spill and produce seeding that leads to early recurrence. In addition, the wall of any associated cyst should be excised along with the tumor. The most friable tumors (melanoma, nonseminomatous germ cell tumors, and some lung cancers) should be isolated with cottonoids prior to

resection to avoid tumor escape into the subdural space.

Because the risk of local recurrence after resection ranges from 15% to 30%, we have recently completed a randomized trial comparing surgery alone with surgery followed by radiosurgery to the margins of the operative cavity. The study showed a significant benefit to using adjuvant radiosurgery, so it has become standard practice at MDACC (when cavity size permits).

General Principles of Intracranial Surgery

In the majority of cases the goal of surgery is resection, either to the maximum possible degree or to a more limited degree for the purposes of decompression and open biopsy. When tumors present in locations preventing safe resection, or the use of prior therapy has raised the possibility of the lesion's representing treatment effect rather than tumor, stereotactic biopsy may be chosen over open resection.

Stereotactic biopsy involves the placement of a biopsy needle under image guidance into a radiologically specified target within a brain lesion. This can be done using a frame-based system or with frameless technology. The latter is now used for almost all cases. A suction-aspiration method is used that pulls small portions of the lesion into the side window at the needle tip, where they are trapped in an inner sleeve that is removed to extract the specimen. Such biopsy is therefore not useful for achieving meaningful resection; if resection is the goal, a craniotomy should be done instead.

In frameless systems, small fiducial markers are placed on the surface of the patient's scalp at multiple points. A scan (usually an MRI) is then performed and the patient comes to the operating room with the markers still in place. The patient is registered to the system by localizing each of the external markers with a reflective wand whose position is determined by the workstation through an infrared detector. This process registers the patient's head into the three-dimensional space predicted by the scan; similar infrared detection is then used on the biopsy needle itself, which effectively becomes the localizing probe. Frameless systems are subject to slightly more error than frame-based systems, and thus should not be chosen for brainstem biopsies, but their accuracy is quite sufficient for biopsy in supratentorial locations.

It is important to recognize that the heterogeneity of gliomas may lead to sampling error if biopsy is not taken from several points within the

lesion. The main risk of stereotactic biopsy is the induction of bleeding at the biopsy site. Most such hematomas are clinically insignificant, but in 1% a craniotomy must be done to relieve pressure from an expanding clot.

The advantage of surgical resection is that it is more likely to overcome the intratumoral heterogeneity (and thus give a more accurate pathologic diagnosis) and of course, it does achieve physical removal of tumor with elimination of mass effect, reduction of ICP, and improvement in neurologic impairment. Intraoperative mapping of cortical function allows the resection of tumors even when located in or near so-called “eloquent” areas, that is, those containing important functions like speech or motor control. It is our routine practice to perform cortical mapping in any patient whose tumor is suspected by radiographic criteria of being within 2 cm of the motor strip, Broca’s area, or Wernicke’s area.

In patients in whom tumor is intimately involved with speech areas, we perform craniotomy awake with anesthesia induced through a laryngeal mask airway during the opening and closing phases of the operation. The anesthesiologist removes the airway (and fully awakens the patient) for the core portion of the procedure when speech mapping and then tumor resection are performed. This is made possible by an extensive scalp block placed after the patient is asleep and lasting for a number of hours beyond completion of the procedure. Speech mapping is done in areas near tumor suggested by preoperative functional MRI as containing speech function. Mapping proceeds as the surgeon applies a low-voltage electrical stimulus to the cortical surface at sites being tested while the patient carries on a conversation or names objects shown on cards. Interruption of speech by the electrical stimulus denotes active function at the site touched. In this way, the completeness of resection can be enhanced while reducing the risk of neurologic injury to maximal degree.

The mortality rate from craniotomy in large series is 1% to 2%. Surgical morbidity includes increased neurologic deficit (8% to 11%), hemorrhage at the operative site (4% to 5%, although no more than 1% require reopening and evacuation), and wound infection (1% to 2%). Medical complications such as deep vein thrombosis, myocardial infarction, and pneumonia occur in 3% to 9%. It is worth noting that venous Doppler studies of patients with glioblastoma before surgery have shown deep venous thrombosis in the legs of 30% to 40% of patients. Thus, the postoperative finding of such thrombosis may simply imply an ongoing hypercoagulable state that predated the surgery. In glioma surgery and in

particular when resecting malignant gliomas, the added risk of an aggressive resection is less than the risk of leaving tumor behind and thereby provoking an ongoing edematous reaction within the residual tumor. Such edema causes worsening of pre-existing deficits and responds only slowly to osmotic dieresis and steroids. In accessible brain tumors, the main constraint on resection is the presence of nearby eloquent brain that cannot be breached without causing a functional decline in the patient.

The use of computer-assisted navigational techniques is optional for most brain tumor cases, but can be quite helpful in minimizing the size of the craniotomy opening and in identifying the extent of the lesion (Fig. 21.4). When such stereotactic navigation is used, four stages are followed: image acquisition, registration, planning, and intraoperative navigation. Typically the images are acquired before the operation after fiducial markers have been placed on the skin of the anterior half of the head. The images acquired are transferred to the intraoperative computer workstation, and can be overlaid on imaging data from functional MRI or tractography to identify anatomic boundaries constraining resection as mentioned above, and thus reduce the risk of neurologic injury. When the patient is placed into final position in the operating room, registration is done to synchronize the patient's fiducial array with the array depicted in the previously acquired images. From that point on the surgeon can check the position of any point within the head in three dimensions relative to the tumor or to anatomical landmarks with accuracy of 1 to 2 mm. This accuracy diminishes, however, as the operation proceeds due to brain shift caused by hyperventilation, CSF loss, and tumor removal. Thus, we generally use intraoperative ultrasound for real-time imaging, as it is cheaper, provides immediate feedback, and is not subject to the vicissitudes of brain shift.

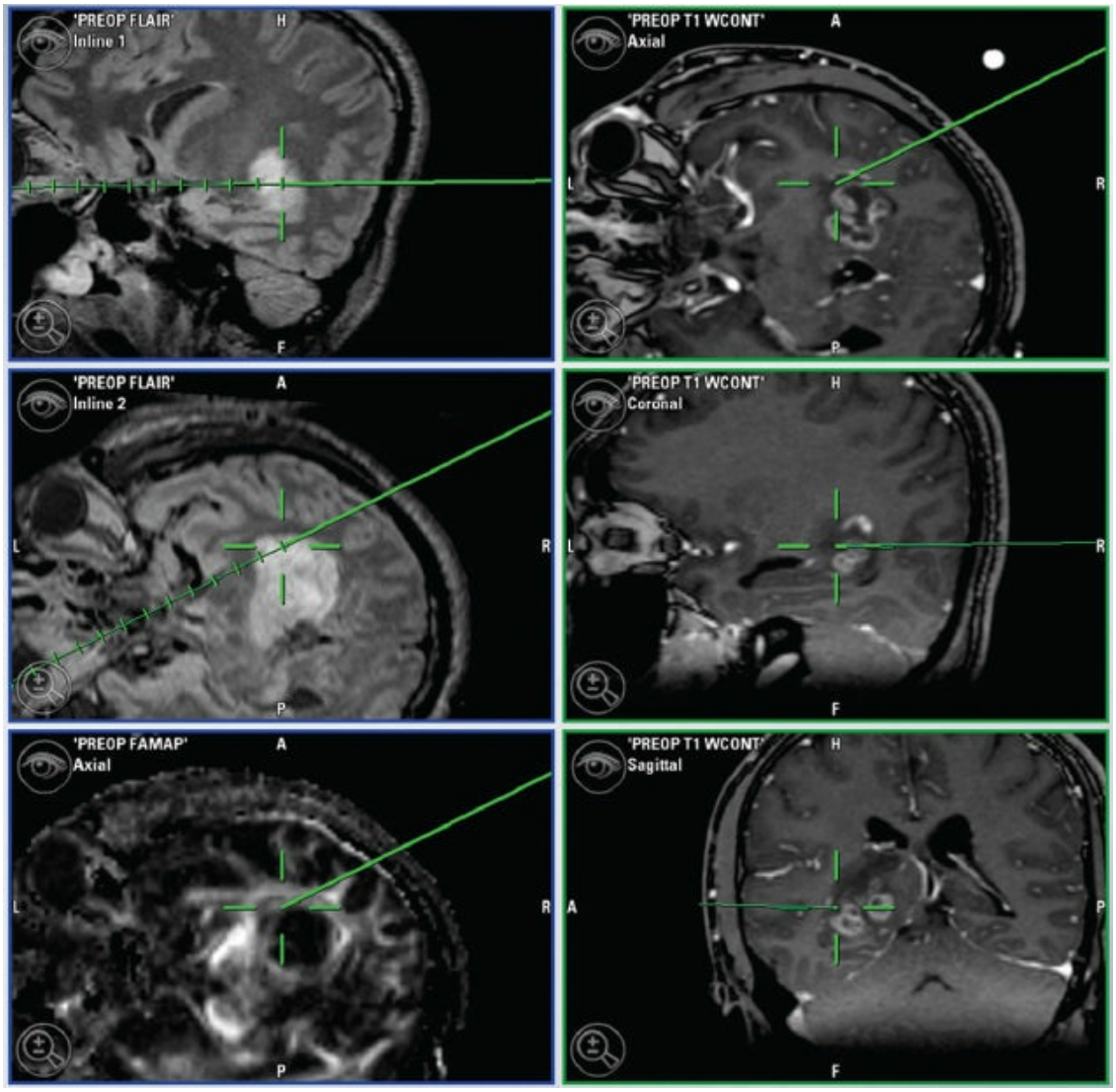

Figure 21.4 MRI acquired before surgery and imported into BrainLab neuronavigational workstation. It shows a glioblastoma in the deep posterior right temporal area, localized by wand guidance that will allow optimal creation of the craniotomy opening and of the transcerebral corridor needed to expose the tumor.

HYDROCEPHALUS

Hydrocephalus is an accumulation of CSF within the head (generally, the ventricles) leading to a rise in ICP that when high enough will compromise brain function. It can be “noncommunicating” when the CSF pathways are blocked somewhere along their course, or “communicating” when the blockage is at the final point of the pathway, that is, the arachnoid granulations near the superior sagittal sinus, where CSF is absorbed into the venous system. Patients with cancer develop hydrocephalus for any of

several reasons:

1. Tumor may be located in the brain near the ventricular system, against which it produces mass effect sufficient to trap the upstream portion and cause it to balloon.
2. Leptomeningeal disease, defined as tumor cells in the subarachnoid space where CSF flow occurs, can clog the absorptive pathways or cause radiographically occult blockage at points of narrowing along the CSF pathways, for example, the aqueduct of Sylvius.
3. The effects of treatment may cause hydrocephalus. The likeliest scenario occurs after whole-brain radiotherapy with formation of scarring either in the ventricles or on the arachnoid granulations that interfere with CSF absorption or flow. Radiotherapy may additionally alter brain compliance and thereby magnify the effects of pathway blockage by shifting the pressure–volume curve.

Treatment

Medical therapies for hydrocephalus reduce CSF production to mitigate rises in pressure. The drugs generally used are Diamox (a carbonic anhydrase inhibitor) and dexamethasone. Both reduce the rate of CSF production but do not increase its absorption, and are temporizing measures useful while preparing a more definitive plan of action. The most direct way of treating hydrocephalus is to remove any mass that causes obstruction. In many patients, however, no such mass exists, and placement of a shunt is the appropriate treatment.

A ventriculostomy is in effect a temporary shunt that diverts CSF out of the ventricle into an external collecting system. This may be placed to record CSF pressures to show whether a shunt is needed, and if so, to help in selecting its valve strength. Indwelling shunts offer a more permanent solution, usually in the form of a ventriculoperitoneal system that runs from the lateral ventricle up through a burr hole into the subgaleal space over the cranium, and thence behind the ear and through the subcutaneous space of the neck, anterior chest, and abdominal wall to a point where it penetrates the peritoneum to deposit CSF into the peritoneal cavity. There the large surface area facilitates efficient CSF absorption. Shunts contain a valve usually located either at the burr hole where the shunt emerges or further downstream above or behind the ear. The valve allows the shunt to provide a set resistance to flow. This mechanism shuts off flow through the shunt when the ICP falls to the desired level, and opens the shunt when

the ICP rises above it.

Patients sometimes require instillation of intraventricular chemotherapy for leptomeningeal carcinomatosis with concomitant hydrocephalus. Such treatment would be ineffective in the presence of a standard shunt, which would immediately flush it from the ventricles. In such cases, we place a shunt with an “on-off” valve that allows the shunt to be closed or opened by external pressure on the valve. Just before chemotherapy is instilled into the ventricular system through an in-line Ommaya reservoir, the shunt is closed. It is reopened after a suitable interval (usually 3 to 5 hours later) to relieve built-up CSF pressure and carry the patient safely until the next treatment. As these patients are usually quite shunt-dependent, longer periods of occlusion are unsafe.

Once an indwelling shunt has been placed, it is expected to function for the remainder of the patient’s life. However, later problems do arise including shunt blockage, infection, or shift in the dynamics of the hydrocephalus that require valve renewal at a different level of resistance. When a shunt is blocked or infected, reoperation is needed to unblock it or remove it. Shunt infection is particularly troublesome as the ongoing hydrocephalus requires “externalization” of the shunt, meaning it is replaced by an external ventriculostomy catheter alone that must then be reinstalled as an indwelling system in a third procedure done only after the infection has cleared. To avoid the necessity for repeat operations done to change out the valve, systems have been developed with adjustable valves in which the setting can be changed by application of a magnetic wand external to the skin overlying the valve. The wand can increase or decrease the valve’s resistance depending on the clinical need. The problem with their use in the cancer setting is that patients with tumor require frequent MRIs, and even during scans of the limbs or torso, such systems can be affected by the magnetic field of the scanner. They must be interrogated, and if necessary reset, after any MRI. Each company’s system uses a different wand device, and the lack of a universal wand makes it hard for patients to transfer care to hospitals that use a system other than the one originally placed. We try to avoid using such systems for these reasons.

In some patients endoscopic third ventriculostomy serves as a substitute for an indwelling shunt. In this procedure an endoscope is inserted through a frontal burr hole and advanced under stereotactic guidance through the lateral ventricle, foramen of Munro, and into the third ventricle. There the surgeon can see the ventricular floor and create an opening that allows

egress of CSF into the subarachnoid space, whence it can be absorbed. This technique is not universally applicable, but it can help patients with hydrocephalus caused by aqueductal stenosis or other compressive etiologies within the posterior fossa. It is not useful in patients with noncommunicating hydrocephalus as the success of the procedure depends on patency of absorptive pathways that are nonfunctional in this scenario.

SPINAL TUMORS

Tumors in the spine form a significant part of neurosurgical oncology and are subcategorized by their anatomic localization. They are either intradural or extradural, with extradural implying an intraosseous location within one or more vertebrae. Intradural tumors are further subdivided into those within the spinal cord, denoted as intramedullary, and those within the space between dura and spinal cord, denoted as intradural/extramedullary. The latter tend to arise from nerve roots or from the dura itself and are usually schwannomas or meningiomas.

Intradural Tumors

Intramedullary Tumors

These form 4% to 10% of all CNS tumors. From their location inside the spinal cord they can affect neurologic function in a variety of ways depending on their precise site of origin and pattern of growth within that very small space. As always, the rate of growth has relevance to the way symptoms develop. Tumors of the cord create symptoms by direct compression of adjacent neural pathways. Because sensory and motor tracts are packed tightly together, either or both can be affected by such compression. In addition, highly vascular tumors in the cord can create neurologic dysfunction by a steal phenomenon, and tumors of any vascularity may provoke formation of a syrinx, that is, a cyst that extends within the cord above or below the tumor, sometimes for great distances. Almost all spinal cord tumors (about 99%) fall within one of three categories, to which we will confine this discussion.

Ependymomas . Ependymomas are the most common intramedullary tumor in adults and make up 60% to 65% of such lesions. They are generally discrete with a distinct interface with the cord and little tendency to invade. Although the histologic appearance of ependymomas of the cord

is similar to that of cerebral ependymomas, their behavior is quite different. Cord ependymomas are much less likely to produce metastases by CSF spread, and rarely convert to malignant forms. Ependymomas of the cord tend to enhance on MRI and grow slowly with an insidious clinical onset (Fig. 21.5). The exception to this comes when they hemorrhage (6% to 8%), in which case a sudden worsening occurs, often associated with neuropathic pain. They can occur anywhere along the cord although they are somewhat more common in the cervical region.

Astrocytomas arising in the spinal cord, like ependymomas, show a different biology from that of their cousins in the brain. Those in the cord are more likely to be well differentiated. Indeed, 90% of them fall into this category as either pilocytic astrocytomas or diffusely infiltrating (but benign) lesions. The infiltrating variety have pure tumor at the heart of the mass, but tend to mingle with normal cord at their periphery and thus are difficult to remove in a truly complete fashion. Pilocytic astrocytomas, similar to those in the brain, are quite discrete and can be removed completely. The main difficulty is identifying the interface with an accuracy sufficient to prevent resection of slivers of normal cord along with the tumor. Only 10% of the intramedullary astrocytomas are malignant and those are overwhelmingly anaplastic in grade. True glioblastomas of the cord occur, but at the minute incidence of 1/20 million people/year.

Astrocytic tumors are more common in children in the spinal cord than are ependymomas (the reverse is true for adults) and 5-year survival varies between 60% and 85% with a 10-year survival of 55%. The mortality may reflect the fallout of profound neurologic deficits imposed by the tumor or transformation to more malignant forms.

The primary mode of therapy for these tumors is surgical removal via laminectomy, dural opening, and myelotomy. Complete resection is achieved in our hands in 90% of ependymomas and is much less likely in astrocytomas. Even with use of intraoperative neurophysiologic monitoring techniques such as somatosensory-evoked potentials and motor-evoked potentials, about half of patients develop new deficits immediately after surgery, but these deficits are transient in all but 10% of those operated on. As the most important influence on the postoperative neurologic status is the preoperative status, patients should ideally be operated before they show neurologic decline. Those with longstanding deficits rarely improve after resection, even when tumor removal is

complete. A recurrence rate of 5% to 10% over 5 years is typical and radiotherapy should not be used in ependymomas of the cord unless (1) gross total resection cannot be achieved despite valiant efforts to do so, or (2) a remnant shows signs of growth while under surveillance by MRI. There is no role for chemotherapy in the treatment of these tumors.

Figure 21.5 MRI (sagittal, postcontrast) of the cervical spine showing a well-defined enhancing tumor within the cord, consistent with ependymoma. Note the syrinx both rostral and caudal to the tumor. This patient presented with quadriparesis

and recovered significantly after total removal of the tumor.

Hemangioblastoma . The third most common category of spinal cord tumor (10%) is the hemangioblastoma. These tumors grow slowly and form 5% to 8% of intramedullary tumors. They often provoke syrinx formation that can be quite extensive (in some cases, even occupying the entire cord), and have a characteristic orange or reddish color due to their extreme vascularity and their content of lipid-laden cells. When a cyst is present, it is often the dominant portion of the mass and the source of compression on the cord. However, even a small hemangioblastoma can provoke a significant expansion of the coronal venous plexus through arteriovenous shunting causing venous hypertension that can itself affect cord function.

These tumors can be solitary or multiple, with multiple hemangioblastomas always denoting von Hippel–Lindau disease (VHL), a genetic tumor syndrome in which renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumor, and hemangioblastoma of the brain are also seen. Thus, patients with one hemangioblastoma should undergo MRI of the entire craniospinal axis to search for others. Eighty percent of patients with hemangioblastoma have VHL, while the remainder represent sporadic cases without a germ-line mutation.

When the hemangioblastoma is removed, care should be taken to interrupt the arterial supply before the dominant draining vein. It can be difficult to sort out which vessel belongs in which category, so a preoperative spinal angiogram may be useful. However, we have found that the discomfort and risk to the patient with angiography outweigh the benefits, and that we can usually tell by direct inspection which vessels are arterial. The tumor is removed by entering its interface with the cord, preferably within the associated syrinx. If no syrinx is present, the surgeon adheres intimately to the tumor capsule and carefully dissects and incises the tumor’s attachments to the cord at the pial surface. Once the tumor is freed from the pia it will tend to extrude slightly from the cord, and the remaining attachments can be divided without difficulty. If the draining vein is taken prematurely, the tumor will swell and the potential for damage to the cord is significant.

Patients who have extensive syrinx show excellent resolution of the cystic changes in the cord if tumor removal is complete. The cord generally continues to show some minor gliotic changes, but the syrinx

will resolve during the 3 months after surgery.

We have found that resection of multiple hemangioblastomas is quite feasible and safe, although tumors located in the anterolateral quadrant pose more risk as the manipulation required to extract them is greater unless a truly lateral approach is taken. However, this is rarely done in intradural surgery to avoid spinal destabilization.

Metastatic Tumors . Metastasis confined within the spinal cord is unusual. Such tumors make up no more than 2% of all cord tumors and are most commonly seen in patients with carcinomas of the breast or lung. Renal cell carcinoma and melanoma also metastasize to the spinal cord with some regularity. The majority of such patients do not undergo surgery because the cord metastasis generally appears during the late stages of the disease when the patient is already somewhat debilitated. As patients with systemic metastasis are living longer, metastasis to the spinal cord is becoming more common, but we still rarely perform surgery on these patients. At MDACC we have operated on intramedullary metastasis because of diagnostic uncertainty or because the patient was in relatively good medical and neurologic condition and preservation of function was sought through surgical decompression. Such tumors usually have an incompletely defined plane with the cord and can therefore be debulked, but not cured, by surgery. Postoperative radiotherapy is typically used, but leptomeningeal dissemination still occurred in 30% of our patient cohort after surgery. No patient with pre-existing leptomeningeal metastasis underwent surgery; it is a contraindication due to the relatively short survival of such patients. In our experience, the median survival after surgery was 5 months, but it is possible to maintain good function during extended survival for up to 4 years.

Intradural/Extramedullary Tumors

These are tumors that occur inside the dura but outside the spinal cord, and thus usually arise from nerve roots or from the dura/arachnoid interface. They are mainly meningiomas of dural origin or schwannomas arising from nerve roots. Each of these tumor types shows excellent delineation from the cord and can be resected completely. The tendency of the schwannoma to arise from a sensory root generally means that the root can be cut with minimal loss of function, as transfer of that function may already have occurred to adjacent sensory roots or because enough

anatomic overlap already exists to prevent a deficit. Some schwannomas extend transdurally into the intervertebral foramen and can be chased there, while others form a “dumbbell” tumor which necessitates resection outside the spine as well as within the spinal canal. Schwannomas have a globular appearance on MRI with a sharp border and moderate enhancement. The presence of a dumbbell picture confirms the diagnosis of schwannoma when it is present. Meningiomas have a different appearance in that they tend to show a tapering, sloping defect with gradual narrowing of the subarachnoid space up to the point of contact between cord and tumor at both its rostral and caudal ends. They tend to be low grade and often calcify. The presence of calcification in a tumor in this compartment is pathognomonic for meningioma. The meningiomas are intimately apposed to the dura into which they may even invade; thus a complete resection may entail dural removal as well.

Metastasis can also be found within the intradural/extramedullary space, usually as drop metastasis from a tumor in the posterior fossa. Almost all patients with this rare phenomenon have known systemic metastasis to other sites, and the diagnosis is not difficult by MRI as the tumor will have an ill-defined and fuzzy border quite different from the typical meningioma or schwannoma. Even so, some patients undergo surgery due to diagnostic confusion; meningiomas and schwannomas are quite curable, so if there is any room for belief that they belong in the differential diagnosis, an operation is indicated. As with intramedullary metastases, metastasis within the intradural/extramedullary space is not curable, but can be debulked. Although this is best regarded as a focal form of leptomeningeal dissemination, the life expectancy of these patients may exceed that of patients with true leptomeningeal spread, so surgery may actually provide benefit in carefully selected cases.

The general surgical approach for intradural/extramedullary tumors is similar to that used for the intramedullary tumors (laminectomy and durotomy), but no myelotomy is necessary. Intraoperative ultrasound localizes tumors nicely in both these categories. In patients who are at risk for swan neck deformity due to tumor impairment of nerves to the paraspinal muscles or because of multiple levels of root involvement, a laminoplasty may be more desirable than a laminectomy to allow better maintenance of spinal stability.

TUMORS OF THE OSSEOUS (EXTRADURAL) SPINE

Patients with tumors within the vertebra present with pain or neurologic deficit, patterns that depend on the level of spine involvement, the degree of root compression, and the degree of mechanical spinal instability. Surgery is more intended to help with diagnosis, palliation, and restoration of spinal stability rather than to achieve oncologic cure, although for primary tumors of the spine cure is a desirable objective. Just as with brain tumors, the multidisciplinary approach is crucial for optimal management of extradural spinal tumors.

Diagnostic Tests

Testing begins with plain x-rays which are inexpensive and easy to obtain, and the results may be diagnostic of tumor. AP and lateral x-rays of the entire spine are also useful in assessing spinal alignment and stability, and can be used to predict the quality of bone strength to be encountered during surgery. The classic findings on x-ray of a spinal bony tumor are loss of pedicle definition (metastases have a heavy predilection for the vertebral pedicle), compression fracture, or destruction of one or more vertebrae with disc preservation; all these features suggest a malignant lesion. However, plain films show an abnormality in only 60% to 80% of patients who have neurologic deficits due to spinal cord compression, and thus merely begin a radiologic investigation of this problem.

Much more useful are MRI and CT in delineating the extent of tumor and the degree of spinal stability. Although MRI provides optimal visualization of epidural compression and paraspinal soft tissue involvement, CT gives better insight into the degree of bony destruction. When metastasis is suspected the entire spine should be imaged to determine the presence of multiple coincident lesions. When MRI is contraindicated (e.g., by presence of a pacemaker) or when images are obscured by artifact (e.g., by prior rod and screw placement) CT myelography can give good imaging of bony anatomy and neural constituents. CT-guided needle biopsy is performed when no prior malignancy exists and pathologic diagnosis is needed. Three-dimensional reconstruction of the CT is quite useful for surgical planning, particularly in those patients who have undergone prior operation in the same region. In those with potential need for spinal instrumentation and pedicle placement, CT is superior to MRI for providing accurate measurement of pedicle dimensions.

MRI is the key to studying spinal tumors completely and accurately.

The degree of spinal cord compression is readily disclosed on T2-weighted images, and fat suppression techniques are quite useful in eliminating overshadowing from epidural or paraspinal fat. MRI is also the most sensitive and specific modality for distinguishing spinal metastases from osteoporotic compression fractures, common among patients with cancer. Osteoporotic fractures are most often seen in the thoracic spine, do not involve the pedicle, and on T1-weighted images lack signal change. Pathologic fractures (i.e., those caused by tumor disruption of bone structure) tend to have a homogeneous signal on T1-weighted images and often involve the pedicle. Radionuclide bone scanning is sensitive but not very specific in detecting metastatic spinal disease. It relies on osteoblastic bone deposition to detect tumor, so rapidly progressive tumors may not be well seen by this technique. It is also relatively insensitive to myelomas limited to the bone marrow. Furthermore, osteomyelitis, hemangiomas, fractures, and even degenerative spondylosis can show as increased uptake on bone scan.

PRIMARY BONE TUMORS

Such tumors are not common, as <10% of all primary tumors of bone involve the spine. They present with symptoms that include night pain, pain at rest (either in the back or as a radicular component), or neurologic deficit. The course can be insidious with relatively nonspecific complaints. Once a lesion is suspected, CT or MRI will typically identify its location and offer clues to its cell type of origin.

Hemangioma

These vascular lesions are found more commonly in females than males, and are solitary two-thirds of the time. They tend to be located in the lower thoracic or upper lumbar spine and have a characteristic honeycomb appearance on plain films due to linear reactive calcification around the radiolucent vascular tissue. Most are confined to their vertebral body and pose no particular clinical issue. Only occasionally do they cause compression of the cord due to extension of the vascular tissue into the epidural space. Pain alone is not an indication for surgery and only those patients in whom neurologic symptoms have occurred are operated on. Asymptomatic lesions can generally be ignored until pain or neurologic deficits develop. Complete resection is possible and surgery is the

mainstay of treatment.

Aneurysmal Bone Cyst

These lesions occur most often in children and are uncommon in patients over 30 years of age. They tend to involve the posterior vertebral elements more than the anterior elements, and the lumbar vertebrae more than other levels. These are benign lesions but can be proliferative and lytic, and occasionally expand rapidly. When they spill into the canal they can cause neurologic compromise. Surgical resection is the favored treatment, sometimes after preoperative embolization. Incomplete resection leads to a high rate of recurrence, but complete resection generally gives long term cure. Radiotherapy is relatively ineffective.

Osteoblastic Lesions

These benign tumors of the spine occur more often in males and are categorized either as osteoid osteomas or as osteoblastomas. The distinction is purely made on the basis of size, with osteoid osteomas being <1.5 cm in diameter. Any young patient with back or neck pain, scoliosis, or radicular pain should be considered for such a lesion. X-rays show a dense sclerotic rim of reactive bone around a small central nidus. They have intense radionuclide uptake on bone scan. The pain caused by these lesions can be treated with nonsteroidal anti-inflammatory agents and occasionally the osteoid osteomas will spontaneously resolve. If pain is an ongoing issue and no resolution has occurred, surgical excision can be performed and if complete, will successfully eliminate the lesion. Osteoblastomas are more likely to come to surgery because of their larger size. Complete tumor removal by en bloc resection is curative. Intralesional debulking is more likely to lead to incomplete resection and thus carries a higher risk of recurrence.

Osteochondroma

These tumors are the most frequently encountered benign lesions of the bone. They consist of cartilage-covered cortical bone with underlying medullary bone. The osteochondroma is formed when the cartilaginous cap undergoes calcification. These are most commonly seen in males in the third decade of life. They also tend to affect the posterior elements

including the pedicle. They have a predilection for the cervical spine. The best diagnostic test for them is a CT scan as they show less radionuclide uptake on bone scan than do other lesions like osteoid osteoma. They tend to increase in size during adolescence and sometimes into adulthood. Malignant transformation is rare and surgical removal is the treatment of choice.

Giant Cell Tumor

These tumors are uncommon, locally aggressive, and occur more often in females. The most frequent spinal location is the sacrum but they can occur anywhere in the spine and usually involve a single vertebra in which an expansile mass has formed. They transform to a malignant state in 10% of cases and then can metastasize. Interestingly, the “giant cells” are not the neoplastic element of the tumor; rather this is usually the other cell component, traditionally believed to be the stromal cells. Thus this tumor is misnamed. The best resection of such lesions is done en bloc as recurrence is more common after intralesional curettage. When found in the sacrum, a sacrectomy (partial or total) with sacrifice of neural elements may be necessary to achieve cure. These tumors are quite vascular and preoperative embolization is useful. They may benefit as well from radiotherapy after a subtotal resection.

Plasmacytoma

These are the most common malignant lesions of the adult spine. Malignant proliferation of the plasma cells occurs in the bone marrow, spleen, and lymphoid tissues. A few patients have a solitary plasmacytoma but multiple plasmacytomas (called “multiple myeloma”) are far more common. Such patients have infiltration of bone marrow by plasma cells with resulting reduction in immunoglobulin levels. However, with solitary plasmacytomas serum protein electrophoresis is normal because the bone marrow is largely functional. Bone in patients with multiple myeloma generally has a poor quality and thus aggressive resections necessitating vertebral reconstruction and instrumentation affixed to adjacent segments are not ideal. The treatment of choice is thus vertebroplasty for pain control and possibly radiotherapy thereafter for tumor control. Half of patients with solitary plasmacytoma progress to multiple myeloma within 5 years (and usually within 3 years), so patients with solitary disease

should be followed closely to detect distant recurrence. Chemotherapy is often used for multiple myeloma, and sometimes stem cell transplant, especially if progression is apparent.

Chordoma

These tumors arise from remnants of the embryonic notochord and tend to be indolent but locally progressive; they can sometimes metastasize. Fifty percent of chordomas occur in the sacrum, 40% in the clivus, and the rest in mobile regions of the spine. The 5-year survival rate ranges from 50% to 75% and the 10-year survival rate is about 50%. En bloc resection is the best currently available intervention for chordoma. For tumors of the sacrococcygeal spine, ventral, dorsal, or combined surgical approaches may be needed together with nerve sacrifice and sometimes resection of adjacent bowel leading to colostomy. Such cases are always done in conjunction with both neurosurgeon and colorectal surgeon, and often with a plastic surgeon as well. There are no current indications for using chemotherapy to manage chordomas, but radiotherapy may have a role. It has been suggested that proton beam irradiation may be especially useful in treating clival chordomas in which an incomplete resection has been done due to the inability to perform en bloc resection in this difficult anatomical area. Resection of clival chordomas requires special skull base techniques, a subject beyond the scope of this chapter but often involving an endoscopic approach through the nasopharynx, with good results when this is followed by proton beam radiotherapy.

Ewing Sarcoma

These tumors are most common in the first two decades of life and occur more often in males. More than half of these involve the sacrum. Plain x-ray shows a lytic lesion with a sclerotic rim. Treatment often starts with chemotherapy with surgery reserved for those patients with an incomplete response or if decompression of the spinal canal is desirable. Radical resection may be necessary here, just as with chordoma.

Osteosarcoma

These are seen occasionally in the spine either as primary tumors or as metastases from sites of origin in the appendicular skeleton.

Osteosarcomas can be primary in young adults, or in older patients they may be secondary lesions arising as a result of radiotherapy to bone. En bloc resection is now advocated followed by radiotherapy and aggressive chemotherapy. Although occasional long-term survival is seen, patients generally die of this disease through widespread metastasis.

Chondrosarcoma

Such tumors are typically indolent and show multiple local recurrences over long periods of time before they switch to a metastatic mode. They are more common in men and have a poor prognosis despite their slow pace of growth. They are quite resistant to radiotherapy and chemotherapy, and thus complete (en bloc) resection is the ideal goal of an operation done for this tumor type.

SPINAL METASTASIS

From 5% to 10% of patients with all types of cancer combined develop symptomatic spinal metastasis at some point during the course of their disease. In one-fifth of patients with involvement of the vertebral column by metastasis, frank spinal cord compression ultimately occurs (Fig. 21.6). The thoracic spine is the most common location for spinal metastasis, with the lumbar spine yielding 20% of cases and the cervical spine 10%. Over half of cases arise from carcinomas of breast, lung, and prostate, due to the fact that these cancers are relatively common and (in the case of breast and prostate cancer) because of their tendency to metastasize to other bones as well. Since pain is the most common symptom, back pain in a patient with known cancer should be assumed to be caused by metastasis until proven otherwise. The pain can be mechanical due to spinal instability from bony destruction or radicular due to nerve root irritation. Pain that worsens with movement and improves when the patient lies down denotes mechanical instability, and suggests that stabilizing instrumentation should be part of any operation done. Although spinal metastasis usually presents with pain rather than myelopathy, a complete neurologic examination is important to detect the latter in any patient suspected of having this condition.

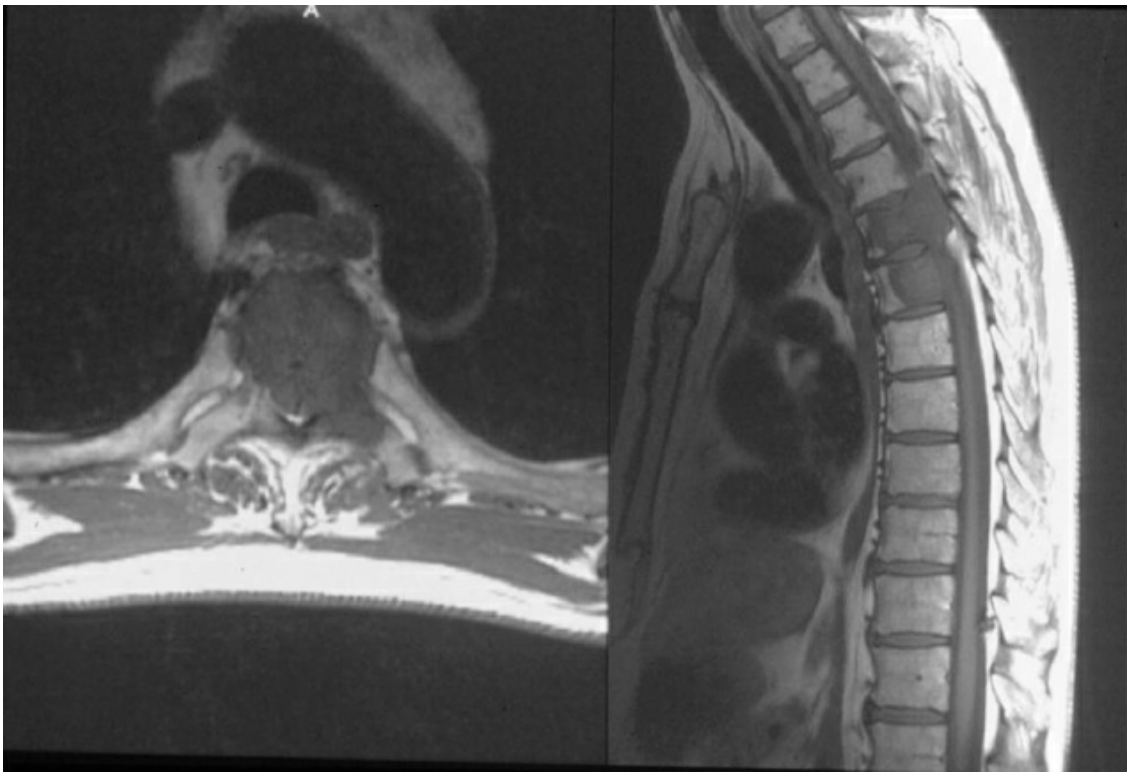

Figure 21.6 MRI (T1-weighted) of thoracic spine of patient with metastatic renal cell carcinoma. The images show (**left**) an axial view at the site of maximum epidural compression. The vertebral body, pedicle, and lamina are involved and the cord is severely effaced. (**Right**) Sagittal view shows tumor in two contiguous vertebral segments (T2 and T3) with the epidural compression caused at T2. Both segments must be resected for long-term local control. This patient requires an operation done by transpedicular approach with reconstruction and posterior instrumentation by a rod-and-screw construct.

The oncologist's weapons for treating metastatic spinal disease include chemotherapy, radiotherapy, and surgery. The most important factor affecting prognosis is the patient's ability to walk when treatment starts. Surgery is palliative in patients with metastatic disease to the spine. The clinical goals should focus on reduction of pain, preservation of neurologic function, and restoration of mobility while maintaining sphincter control. Loss of such control predicts a poor outcome. The debate over the relative efficacy of radiotherapy versus surgery is complex and continues today. However, a patient in relatively good shape from the medical and oncologic perspective with a reasonable life expectancy overall (>6 months) should be considered for surgery if spinal metastasis endangers neurologic function but has not yet eroded it. In addition, pain of

instability (axial loading pain) will be helped more by resection and stabilization than by radiotherapy, which controls the tumor but leaves the mechanical instability in place. The goal of surgery is to provide decompression of the spinal cord and nerve roots and/or to stabilize the spinal column. Radiotherapy is a good modality, however, for treating radiosensitive spinal tumors or those causing minimal or no neurologic deficits. We have found that stereotactic radiosurgery for spinal metastases can be quite effective in suppressing focal deposits of disease with good safety to the nearby cord, and that it shortens the time of treatment significantly without compromising effectiveness. Radiosurgical delivery requires five or fewer sessions, while standard external beam irradiation is given in 10 fractions to a total dose of 30 to 40 Gy.

Metastatic breast cancer is typically radiosensitive and also can respond to hormonal therapy, cytotoxic chemotherapy, or both. Thus, in breast cancer cases (and in particular those with multiple spinal lesions) surgical intervention is limited. Spinal involvement from a lung cancer can result from direct extension of a tumor from the chest wall to the nearby spine, or may develop from hematogenous routes. Superior sulcus tumors in particular can involve the spine and require intricate cooperation between thoracic surgeon and neurosurgeon for ideal resection of the lung, chest wall, spinal, and occasionally neural components, with reconstruction of the chest wall needed in many cases. Because of its high degree of radiosensitivity, small cell carcinoma rarely needs surgery. Prostate cancer also responds more often than not to palliative efforts without surgery and is sensitive to radiotherapy at least for a time. Its spinal involvement tends to be multifocal, and thus surgical cases must be carefully chosen. The role of surgery in prostate cancer tends to focus on correction of spinal instability, control of intractable pain caused by a focal lesion, or prevention of neurologic decline.

The nonsmall cell carcinomas of the lung (squamous cell carcinoma and adenocarcinoma) can metastasize to the spine and are resistant to radiotherapy. Although surgery can be considered for such patients, they often have poor pulmonary function in which case a transthoracic approach is less desirable. Transpedicular approaches through a midline posterior incision are preferred for them or indeed for any patient with a significant burden of lung metastasis compromising pulmonary mechanics. The more concentrated dosing allowed by stereotactic delivery of radiotherapy to the spine may yield better control than that achieved by

standard radiotherapy. Renal cell carcinomas also resist radiotherapy and the systemic disease varies significantly in its clinical behavior. In many patients the pace of the disease is relatively indolent even when lung or other metastases are present. Renal cell carcinoma thus lends itself to surgery, but it is quite vascular and preoperative embolization is often helpful in limiting intraoperative hemorrhage. The key to resection of a renal cell carcinoma from the spine is a quick removal after a careful and comprehensive isolation of the tumor and as much devascularization as possible prior to tumor entry. Such tumors must usually be removed in piecemeal fashion and bleed significantly during that removal. When the tumor has been removed completely or almost so, the bleeding slows and stops, or at least becomes much more responsive to the usual topical control measures.

INDICATIONS FOR SPINAL SURGERY

Because patients with vertebral column tumors usually have a life expectancy limited to 1 to 2 years, and may have multiple sites of disease when the tumor is metastatic, oncologic cure is not the usual goal of an operation. The benefits must be balanced against the risks of a major procedure and the time needed for recuperation, usually 4 to 8 weeks. Thus, a patient with 3 to 4 months of predicted survival would not be a good candidate for such an operation as it would consume half his remaining life span in recovery time. Thus, the goals of surgery are dictated by the patient's life expectancy, functional (including neurologic) status, tumor type, chance for oncologic cure, degree and type of pain, degree and duration of compression of spinal cord or nerve roots, and the need to restore spinal stability.

The classic indication for surgery is rapid neurologic decline due to epidural compression of the spinal cord caused by a radioresistant tumor. Spinal instability is a commonly cited reason as well, but there is no uniformly accepted definition of that phrase. Commonly used definitions include disruption of two of the three bony columns of the thoracolumbar spine (although this does not apply to the cervical spine, whose structure is different); kyphotic deformity >20 degrees; or loss of >50% of vertebral body height in any portion of the spine. If patients meet one or more of these criteria and have a well-defined syndrome of axial loading pain, then surgery is a reasonable consideration as vertebral resection and reconstruction with appropriate anterior and/or posterior instrumentation

may give excellent pain relief long term. Restoration of sagittal balance (allowing correction to comfortable, erect, energy-efficient posture) in patients with kyphotic deformity, significantly improves the quality of life.

Overall the aims of spinal surgery are three in number. These include: (1) decompression of the spinal cord to improve or maintain neurologic status, (2) decompression of nerve roots to reduce radicular pain, (3) stabilization of the spine to reduce the pain of instability, and (4) correction of kyphotic or scoliotic deformities impairing sagittal/coronal balance, or loss of vertebral height that add to the patient's pain burden.

Surgical Adjuncts

Embolization done prior to surgery (within 24 hours) can reduce blood loss during operations and may be useful for hypervascular metastases like renal cell carcinoma and thyroid carcinoma. Bleeding from thyroid carcinoma is the most profound and difficult to stop of any metastasis, and such tumors should be approached surgically with great caution and with an adequate supply of blood readily available. Embolization requires spinal angiography which carries risk and some discomfort to the patient. The embolization itself can cause spinal cord infarction and complete paralysis should the injection be done too proximally within the vascular tree. This procedure should only be performed by interventional neuroradiologists expert in its application.

Blood loss during resection of spinal metastases ranges from minimal to extreme. If large blood loss is expected, transfusion should begin as soon as tumor resection starts to avoid having to play "catch-up" and to prevent hemodynamic instability. Patients who have received multiple transfusions will take longer to recover and may be in the hospital for several weeks after the surgery. We do not advocate the use of cell savers out of concern that they may re-circulate malignant cells into the bloodstream. Cryocoagulation of the tumor in situ can be very effective in stopping intractable bleeding, but the cord must be excluded from the zone of freezing.

We routinely perform intraoperative monitoring of somatosensory-evoked potentials and motor-evoked potentials, which give immediate feedback on the integrity of neural pathways in the dorsal and ventral portions of the spinal cord respectively. When motor-evoked potentials are used, anesthesia techniques must be modified to exclude paralytic agents.

Fluoroscopy is useful for localizing vertebral levels early in surgery. It

also helps to ensure good screw placement during spinal fixation, with avoidance of pedicle breach or penetration of the vertebral endplate or cortex by a misdirected or overly long screw.

Surgical Techniques

Extradural spinal metastases can be approached from an anterior, posterior, or combined direction. The choice of approach is determined by tumor location (vertebral body vs. posterior elements), the spinal level, the extent of the tumor, and the degree of patient debility. When tumors involve only the posterior spine and laminae, decompression is done through a posterior laminectomy approach. However, it is more common to see the compression along the anterior aspect of the thecal sac, in which case effective decompression can be achieved either via an anterior/anterolateral or a posterolateral (transpedicular or costrotransversectomy) approach. When the dural sac is surrounded by tumor from all directions, resection proceeds either by the posterolateral transpedicular method or by combined anterior and posterior approaches.

The anterior approach is awkward at the highest cervical and thoracic levels (C1, C2, and T1–T3) and the lowest lumbar and sacral segments (L5 and below). Access to the upper cervical spine can be done through a transoral or mandibular splitting approach but these are technically difficult procedures and in the context of malignant disease may be unrealistic for palliation. The high thoracic segments can be reached by performing a sternal split with reflection of the first and second ribs laterally. The heart and great vessels limit caudal exposure as does the natural spinal curve. We have preferred to approach tumors in these locations purely from a posterior transpedicular direction. The lumbosacral junction can be reached from the front without great difficulty, but stabilization at this level is difficult and requires complex posteriorly placed lumbo-pelvic rod constructs; thus such operations are always done as combined anterior–posterior cases. Sacral reconstruction is essentially impossible although replacement of the L5 vertebral body can be performed.

Spinal stabilization is needed after any anterior corpectomy and after most (but not all) posterolateral decompressions. When two or more vertebral body segments have been removed, anterior fixation alone is usually insufficient for long-term stability and supplementation with posterior rods and screws is helpful. The current posterior instrumentation

systems are highly developed and allow stabilization anywhere from the occipitocervical area to the lumbar spine. Lumbo-pelvic fixation remains a difficult area in which the perfect construct has not yet been achieved.

Patient debility plays an important role in selecting surgical approaches. Many patients have undergone previous radiotherapy, and surgery performed through an irradiated field carries a higher risk of wound complications. Thus, plastic surgical assistance can be quite helpful for wound closure in such patients.

In patients whose debility or overall physiologic impairment make wound healing problematic, laser interstitial thermal therapy is an alternative to open spinal surgery. This involves stereotactic placement of a thermal probe into a tumor targeted for ablation (Fig. 21.7). Under real-time thermal imaging in an intraoperative MRI suite, the lesion is heated to >45° to induce cell death and tumor shrinkage. At MDACC we have used this method to achieve not only tumor control but also decompression of spinal cord distorted by adjacent tumor. In addition, new minimally invasive methods for placing spinal instrumentation are gaining ground in spinal oncology, and allow spinal stability to be restored without lengthy incisions requiring prolonged convalescent times and pain due to paraspinal muscle trauma. Such techniques have promoted postoperative mobility and recovery in the select group of patients in whom they can be used effectively.

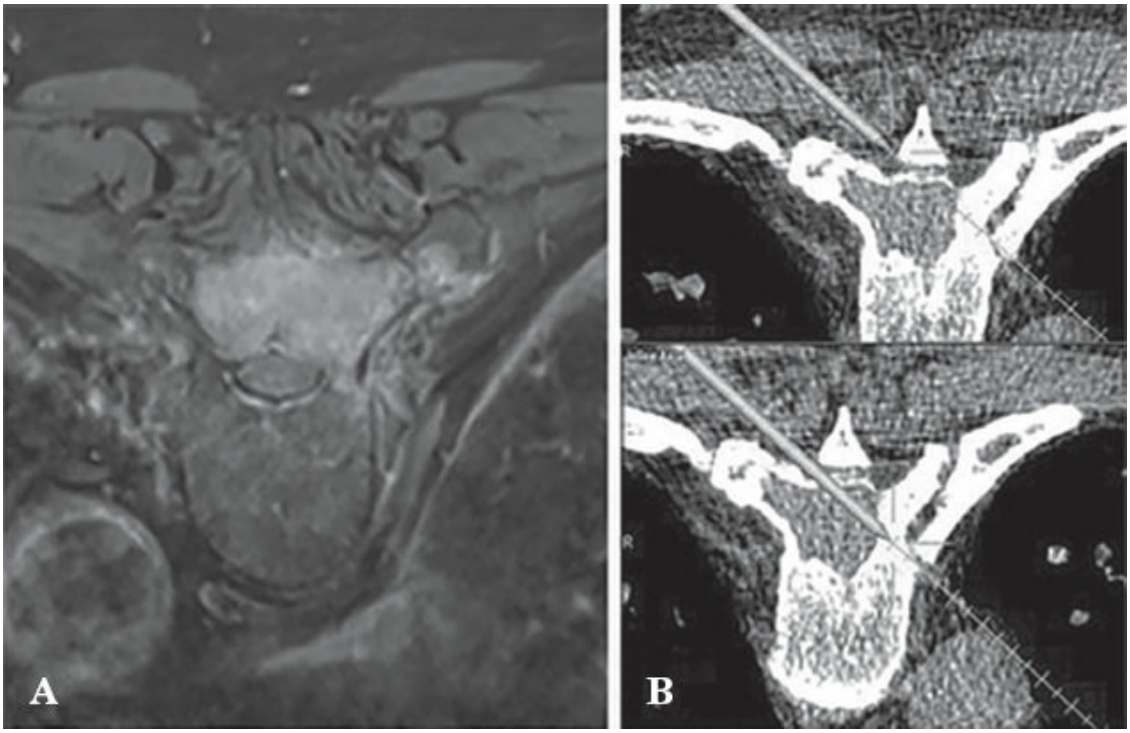

Figure 21.7 Laser interstitial thermal therapy. **A:** Renal cell carcinoma of spine in posterior elements of T9 with incipient cord compression, as shown in MRI (T1-weighted, postcontrast, axial). **B:** Thermal probe placement on cognate CT slices through the same tumor. The tumor will be heated at this safe location to avoid thermal damage to the nearby spinal cord.

Vertebral replacement can be done with autologous or allograft bone cut to appropriate size, methylmethacrylate, or an expandable titanium alloy cage. We use expandable cages for the majority of our vertebrectomy patients as they permit adjustment in situ which can restore lost vertebral body height without drilling into the adjacent vertebral bodies, as must be done to anchor a methylmethacrylate strut graft. However, a number of patients still receive methylmethacrylate grafts when expandable cages will not fit the bony defect or when the corridor of access to the vertebrectomy site is offset and prevents placement of the tools necessary for cage expansion. We are least likely to use a bone graft because long-term fusion is not generally necessary in a patient population whose life expectancy rarely extends beyond 2 to 3 years, and in which strenuous physical activity is not common.

Multidisciplinary cooperation between surgical services is frequently necessary in performing these operations. It is routine to engage the services of a thoracic surgeon for anterolateral approaches to the thoracic spine needing thoracotomy or a thoracoabdominal approach for spinal tumors near the diaphragm. Retroperitoneal or transabdominal approaches require the services of a general surgeon, and complex neck approaches from an anterolateral or posterolateral angle may benefit greatly from help by a head and neck surgeon. Although brain operations are exclusively the province of the neurosurgeon, spinal procedures can involve any of these named services as well as plastic surgery when significant tissue loss has occurred that compromises wound closure, or when the effects of prior treatment make wound healing tenuous.

Cervical Spine

High cervical (C1 and C2) vertebral tumors can be approached transorally with or without transmandibular modification, depending on the degree of rostral extension of the tumor. This approach is destabilizing and mandates posterior occipitocervical fixation as part of the procedure. Tumors in the anterior portion of the subaxial cervical spine can be approached through

the anterolateral neck along the edge of the sternocleidomastoid muscle. This provides excellent exposure but puts the function of the recurrent laryngeal nerve at risk through potential stretch injury. To avoid postoperative hoarseness, retractors should be relaxed at 30-minute intervals throughout the case. En bloc resection in the cervical spine is challenging and usually not possible due to the anatomic constraints imposed by the vertebral artery, nerve roots, and spinal dura.

Thoracic Spine

Tumors in the T1 vertebral body that do not extend laterally can be approached through an incision in the low anterolateral neck, but many cannot be well exposed without sternal split (trapdoor approach). Thoracic vertebral tumors with a lateral paraspinal extension require posterolateral thoracotomy from the side of greatest tumor bulk. Transpedicular vertebrectomy is useful for tumors in this region but will usually not clear the disease as effectively as the transthoracic approach. Because the transpedicular method is facilitated by bilateral transection of nerve roots it is usually not used at T1, where the roots may be important for hand function.

Thoracolumbar Spine

Direct exposure of a thoracolumbar (T10–L1) vertebral tumor requires a thoracoabdominal approach in which a portion of the diaphragmatic crus is divided to uncover the spine not only over the tumor site, but also over adjacent levels needed for fixation of an anterior plate-and-screw construct. The side of the approach is decided by the location of the tumor within the vertebral body; those extending equally to both sides are approached from the left to avoid the liver. En bloc resection of tumors in the thoracic, thoracoabdominal, and lumbar spine is challenging but is being used more as surgeons become familiar with this special technique.

Lumbar Spine

For vertebral tumors below L1 a retroperitoneal approach is favored. Transpedicular vertebrectomy in this region is difficult because of the larger size of the vertebral body and the obstruction by nerve roots that cannot be transected as they control leg strength and sensation. L4 and L5 are often best approached from an anterior direction because of obstruction of direct lateral access by the ilium, the extent of which varies from patient

to patient.

Sacrum

Tumors in the distal sacrum (S3 and below) can be approached solely from the back, usually without need for reconstruction, stabilization, or sacrifice of bowel or bladder function. Maintenance of such function requires that both S2 nerve roots be kept intact as well as one S3 nerve root. High sacral tumors (S1 and S2) require complete sacrectomy. This is a technically challenging and usually staged procedure with a total surgical time exceeding 24 hours and using the talents of multiple surgical services. Rehabilitation after total sacrectomy takes at least 3 months and the hospital stay is lengthy.

Postoperative Radiotherapy

Although en bloc resections are now being done in selected cases, most patients undergo removal of spinal metastasis by intralesional debulking. Although removal may appear complete both at the time of surgery and on postoperative imaging, microscopic disease almost invariably remains. Therefore, postoperative radiotherapy is given in most patients who have not previously undergone irradiation of the site. When used before surgery, radiotherapy is associated with infection and other problems of wound healing in one-third of patients. However, newer intensity-modulated methods and stereotactic radiosurgical techniques may allow tumor control without imposing such regional tissue compromise.

TUMORS OF PERIPHERAL NERVE

Tumors may arise on peripheral nerves anywhere that peripheral nerves go. Thus such tumors can be found anywhere in the extremities, trunk, soft tissues of neck and scalp, or on the skin surface. Most are benign and are identified either as neurofibromas or schwannomas. Solitary tumors such as are often found in the paraspinal region are typically schwannomas. When tumors are multiple, neurofibroma is the more likely diagnosis.

Neurofibromas can be either solitary (intraneural), diffuse (cutaneous), or plexiform (involving several nerve branches). Solitary neurofibromas are the most commonly encountered benign tumors of the peripheral nerve. They are slow growing and relative circumscribed lesions that cause pain, and less often sensory loss or weakness when they grow to large size. Solitary neurofibromas are not linked to a genetic disorder, but multiple

neurofibromas indicate the presence of NF1, caused by loss of function of the *NF1* tumor suppressor gene from chromosome 17. Diffuse neurofibromas occur on the skin and in subcutaneous tissue of children and adolescents, and often are associated with NF1. Plexiform neurofibromas are pathognomonic for NF1 and appear as a fusiform and often quite large expansion of nerves in the extremities, face, or trunk. They can affect the brachial plexus or the lumbosacral plexus. When superficial they can cause cosmetic deformity to a distressing degree, and when a limb is affected, substantial expansion can compromise venous return and limb function.

Schwannomas are benign and slowly growing, well-encapsulated tumors composed of neoplastic Schwann cells in a collagenous matrix. They are the second most common tumor involving peripheral nerves and usually occur in patients between 30 and 60 years of age. 20% are found along the median, ulnar, or radial nerves. These tend to cause a mild (or no) neurologic deficit, but pain can be a significant component of the clinical presentation. The classic distinction between neurofibromas and schwannomas holds that schwannomas are likely to arise from a small number of fascicles within the nerve, whereas neurofibromas arise more diffusely in the nerve and thus are more difficult to tease out surgically without nerve sacrifice.

Figure 21.8 Intraoperative view of neurofibroma after its separation from the tibial nerve. The entering and exiting fascicles remain connected to the tumor, but are divided at this point to free the tumor. This approach allows preservation of most of the nerve, which courses around the tumor outside its capsule and remains connected and functional. This patient has NF1 and suffered no deficit from the removal.

In our experience schwannomas can usually be resected without sacrifice of nerve function by performing an intracapsular shelling out of the tumor (Fig. 21.8). Since these tumors are almost always histologically benign, any small remnants left behind in the approach rarely re-establish themselves to form recurrent tumor. Often the tumor arises from only one or two fascicles of the several hundred that make up the nerve, with most of the nerve bypassing the tumor albeit in a somewhat distorted course. Neurofibromas appear to arise from a larger numbers of fascicles, although many of them have four feeding fascicles or fewer. Thus, they too can be resected in similar fashion with similar likelihood of preserving nerve function. Some neurofibromas run diffusely through the nerve as per the classical description, but the majority do not. Therefore, identity of a tumor as a neurofibroma should not preclude an attempt at resection as the nature of the tumor's origin and its resectability can only be determined at the time of surgical exposure.

Mutation of the *NF1* gene provokes the formation of neurofibromas. However, the alterations imposed by this syndrome are not limited to the induction of nerve sheath tumors. Patients are prone to have optic gliomas and frequently have short stature, neuropsychological abnormalities, a higher incidence of mental retardation, and dysplasia in the axial and appendicular skeleton as well as the skull. They have a higher incidence of intracranial glioma, usually astrocytoma, and of spinal cord ependymomas. The diagnostic criteria for NF1 (and for NF2) are given in Table 21.6.

TABLE **21.6** Diagnostic Criteria for NF1 and NF2

Neurofibromatosis Type 1

Patient has two or more of the following:

- Six or more café-au-lait spots
  - >1.5 cm in postpuberty
  - >0.5 before puberty
- Two or more neurofibromas of any type or at least one plexiform neurofibroma
- Freckling in axilla or groin
- Optic glioma
- Two or more Lisch nodules (hamartomas of iris)
- One or more distinctive bone lesions, e.g., sphenoid dysplasia or thinning of cortex of long bone
- One or more first-degree relatives with NF1

Neurofibromatosis Type 2

Confirmed NF2 has:

- Bilateral vestibular schwannomas
- or
- Family history of NF2
- plus
- unilateral vestibular schwannoma at age <30 years or one or more of the following:
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular cortical opacities (in eye)

NF2 is a separate, much less common, and somewhat misnamed condition caused by a completely different gene defect on chromosome 22. Patients with this disease do not get neurofibromas at all, but schwannomas that largely affect cranial nerves. They are also susceptible to the development of multiple cranial or spinal meningiomas and have some risk of developing intracranial glioma. The pathognomonic lesion of NF2 is a bilateral vestibular schwannoma leading to loss of hearing.

The malignant form of each of these tumors is termed a *neurofibrosarcoma*, or malignant peripheral nerve sheath tumor (MPNST) as a more general descriptor. Although most schwannomas do not transform to a malignant tumor, melanotic schwannomas have a 10% chance of such transformation. For patients with NF1, the chance of developing an MPNST over the course of their lifetime is 10%. Such tumors are highly aggressive, invade locally, and can metastasize. Chemotherapy is ineffective, radiotherapy is palliative, and the main hope for treatment is early detection with a radical surgical removal. Two-thirds of MPNSTs arise from neurofibromas, usually in a patient with NF1. The 5-year survival rate is 15% to 20% in this category. Sporadic MPNSTs not associated with NF1 have a somewhat better survival rate with a 5-year

survival rate of 50%. It is possible to acquire an MPNST after exposure of the nerve to external beam irradiation. The treatment of these tumors, whatever their origin, is surgery and this can be performed either as radical amputation of the involved limb, sparing of the limb with transection of the involved nerve, or selective resection with nerve sparing analogous to that performed for benign nerve sheath tumors. Although it is logical to suggest more radical strategies given the malignancy of this tumor type, we have had success in occasional patients treated with intracapsular resection because the MPNST may occupy only the core of the benign neurofibroma in which it arose, and which has maintained benign histology around its periphery. Using this strategy, we have achieved recurrence-free survival exceeding 10 years in some patients. Thus, we do advocate using this approach to give the patient at least a chance of retention of function, and save more aggressive resection for a second operation done for local recurrence.

In the past 5 years the classical categories of NF1 and NF2 have been joined by a third category, schwannomatosis. This occurs in patients with mutation of the *INI1* gene located on chromosome 22q at a separate locus from the *NF2* gene. Such patients have multiple schwannomas in peripheral, spinal, and cranial nerves. About one-third have segmental schwannomatosis limited to a single region of the body. Bilateral vestibular schwannomas have not yet been described in this disease, but unilateral involvement of the vestibular complex has been noted in a few patients. Schwannomatosis is not associated with learning disability and cannot be diagnosed without first ruling out the presence of a mutation in the *NF2* gene. Such patients present with pain syndromes which are quite amenable to relief by surgical resection (with nerve sparing, as above) of the offending tumor or tumors.

Recommended Readings

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22 Cancer of Unknown Primary Site

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INTRODUCTION

Cancer of unknown primary site (CUP) is a heterogeneous group of cancers that comprises 3% to 4% of new cancer diagnoses and can pose a therapeutic challenge. Although chemotherapy is the primary treatment modality in patients with CUP, the surgeon may play an important role in both the diagnosis and the treatment of these patients. In particular, surgeons are often asked to evaluate patients with cancers that present as solitary metastases (lymph node(s) or liver as common presentations) or as carcinomatosis.

In this chapter, we discuss the presentations and clinical features of CUP; outline a practical approach to the diagnostic evaluation of patients with CUP—including the role of tissue of origin molecular profiling and next-generation sequencing (NGS) in the era of sophisticated immunohistochemistry; discuss the role of surgery in various clinical scenarios; and briefly explore novel chemotherapeutic and immunotherapeutic treatment options.

DEFINITION AND GENERAL CONSIDERATIONS

CUP is defined by the presence of a biopsy-proven cancer for which the anatomical origin of the primary tumor is not revealed after a thorough history and physical examination The prevailing hypothesis in CUP is that the primary tumor either remains microscopic and escapes clinical detection or disappears after seeding the metastasis, which may be due to angiogenic incompetency of the primary tumor.

These tumors are often grouped according to histologic subtype, including squamous cell cancer, adenocarcinoma (including poorly differentiated adenocarcinoma), poorly differentiated or undifferentiated carcinoma, or undifferentiated neoplasms (the name given to a

heterogeneous group of tumors of various cell origins). Table 22.1 lists the frequencies of each subtype (adenocarcinoma is the most common).

As found in a large series, the most common locations of CUP metastases are the lymph nodes, bones, lungs, liver, and the peritoneum. Other metastatic sites include brain, meninges, pleura, subcutaneous tissues, adrenal glands, and kidneys.

In most patients, the site of origin of the metastatic disease is never discerned. In few, a latent primary tumor is eventually identified during the lifetime of the patient through clinical examinations, surgery, or autopsy. Older studies report that the primary site is identified during the patient's lifetime in only 25% of CUP cases; this number is lower with sophisticated imaging techniques (where baseline studies have been negative). Metastases from squamous cell cancers typically originate in the head and neck region or the lungs, whereas metastatic adenocarcinomas originate in the lungs, breasts, thyroid gland, pancreas, liver, stomach, colon, or rectum. As depicted in Figure 22.1, a patient can present to a CUP clinic with true CUP (no primary cancer found on a focused but thorough evaluation) or sometimes with an uncertain final diagnosis (new cancer vs. recurrence in a patient with history of previously treated cancer). Additionally, it is not uncommon to see patients with metastatic cholangiocarcinoma in a CUP clinic given the nonspecific imaging and pathologic findings although increasingly physicians are able to make the distinction between the two, with better imaging criteria and known patterns of spread (lungs, bone, and omentum).

TABLE 22.1 Histopathologic Subtypes of CUP

Histopathology	Percentage of CUP Patients
Adenocarcinoma (including poorly differentiated adenocarcinoma)	60
Squamous cell carcinoma	5
Others:	35
• Poorly differentiated carcinoma	
• Poorly differentiated neoplasm	
• Unclassified neoplasm	

CUP, cancer of unknown primary site.

The median survival of patients with CUP is 6 to 9 months. Specific subgroups of patients with metastatic CUP, such as those who are able to be treated with appropriate therapy, have considerably better prognoses than the group as a whole. This favorable cohort includes patients with squamous cell cancer metastatic to cervical lymph nodes, women with metastatic adenocarcinoma in axillary lymph nodes, men with undifferentiated cancer and elevated β-human chorionic gonadotropin (β-hCG) or α-fetoprotein (AFP) levels, women with peritoneal carcinomatosis, and patients with neuroendocrine CUP. These subgroups are discussed later in this chapter in more detail.

The therapeutic goal in evaluating patients with CUP is to identify those patients for whom a cure or effective specific therapy is an option. In addition, local therapeutic options can potentially help with adequate disease control and palliation in selected patients.

HISTORY AND PHYSICAL EXAMINATION

In patients with CUP, a complete history and physical examination are essential. An individual history of malignancy or a family history of cancer may guide the physician in establishing the site of an occult primary tumor.

During physical examination of a patient with CUP, several anatomical sites warrant particular attention. The head and neck should be examined thoroughly, particularly when a diagnosis of squamous cell cancer has been made. This includes examination of the oropharynx, hypopharynx, nasopharynx, and larynx, typically assisted by indirect or fiberoptic laryngoscopy. The thyroid gland should be examined for enlargement or asymmetry. All nodal basins, including those of the head and neck and the supraclavicular, axillary, and inguinal regions, should be examined for palpable or enlarged lymph nodes.

In women, a careful breast examination and a thorough bimanual pelvic examination should be performed. For men, testicular and prostate examinations are particularly important. All patients should undergo a thorough skin examination and rectal examination.

LABORATORY STUDIES

Routine tests such as complete blood cell count, chemistry studies, and liver function tests should be performed in all patients, and stool should be

checked for occult blood if the patient is anemic or symptomatic. Beyond these basic tests, the clinical laboratory has limited usefulness in the diagnostic evaluation of patients with CUP, but additional studies should be requested on the basis of histologic and radiologic findings. Serum tumor markers, although not specific enough to make a diagnosis, are helpful in following a patient's progress on treatment.

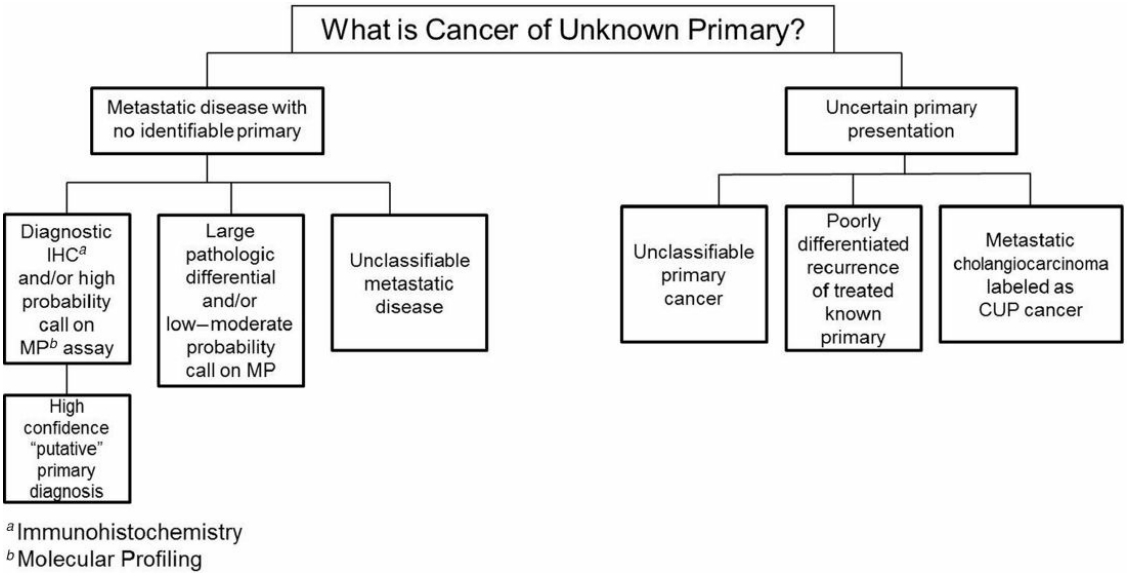

Figure 22.1 Diagnostic challenges to identify tissue of origin contribute to CUP.

Radiographic Evaluation

Radiographic evaluations of patients with CUP should be focused on identifying the primary tumor and delineating the extent of metastatic disease.

CT Scan of the Chest, Abdomen, and Pelvis

When not contraindicated due to renal dysfunction or contrast allergy, CT scan of the chest, abdomen, and pelvis, with intravenous iodine-based contrast is essential to the work up of a CUP patient, because it can help in locating the primary tumor, evaluating the extent of disease, and selecting the most accessible biopsy site.

Mammography

Women with adenocarcinoma and of childbearing age or older,

particularly those with metastatic adenocarcinoma, should have undergone mammography within a year. Unfortunately, identifying subtle radiographic abnormalities is difficult in younger women, who often have extremely dense breast tissue. If the mammogram and breast sonographic findings are negative, magnetic resonance imaging (MRI) of the breast is indicated in women who present with isolated axillary adenopathy.

Magnetic Resonance Imaging

MRI may be indicated if CT with intravenous contrast is contraindicated. As mentioned previously, the most defined role of MRI in CUP is in women who present with isolated axillary lymph node metastases and suspected occult primary breast carcinoma. The results of several studies suggest that MRI of the breast can help with tumor detection in up to 75% of patients. This result can influence surgical management, with a negative breast MRI predicting a low yield at mastectomy.

Positron Emission Tomography

The role of positron emission tomography (PET) scan using ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG PET) is controversial for initial evaluation of "all-comers" with CUP cancers. PET imaging is recommended in patients with occult primary head and neck cancer presenting with squamous cell carcinoma (cervical CUP) and in select patients who present with a solitary potentially resectable CUP lesion. Several recent small studies have described the role of PET in patients who present with cervical CUP. The advantages of locating the primary tumor in patients who present with cervical lymphadenopathy (occult head and neck cancer) are smaller postoperative radiation ports that can decrease early and late complications, better surveillance for recurrence, and improved prognostic determination. A review of 16 studies (1994 to 2003) of 302 patients with cervical lymph node metastases from unknown primary tumors by Rusthoven et al. demonstrated that PET can assist in detecting unknown primary tumors and/or previously undetected regional or distant metastases compared to conventional workup, including panendoscopy, CT, or MRI. The sensitivity, specificity, and accuracy of PET to detect unknown primary tumors in patients with cervical lymph node metastases were 88.3%, 74.9%, and 78.8% respectively. FDG-PET identified 25% more primary tumors and 27% more regional or distant metastases than

conventional workup in these patients.

In general, an exhaustive search for the primary tumor site in these patients by radiographic evaluation can be expensive, inconvenient, and anxiety provoking for patients and often has no significant effect on patients' therapy or the ultimate course of their disease. However, PET is a beneficial modality in CUP patients who have primarily osseous disease, since it can be used to monitor response to therapy unlike bone scan or CT.

Pathologic Evaluation

Fine-needle aspiration (FNA) biopsy has largely replaced core biopsy as the first pathologic test. This can be followed by core biopsy, incisional biopsy, or excisional biopsy as needed for more specific histologic identification. Good communication between the clinician and the pathologist is important, because details of the history and physical examination can influence the pathologic review and facilitate submission of additional tissue, if necessary, for an accurate diagnosis.

Light Microscopy

Light microscopy (hematoxylin and eosin staining) is ordinarily sufficient to determine the cell of origin. About 60% of CUP are found to be adenocarcinoma on light microscopy. An additional 5% are squamous cell carcinoma, and the remaining 35% are diagnosed as poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm. Electron microscopy, which helps identify the ultrastructural features of the cell of origin, is rarely needed. For example, desmosomes and intracellular bridges are associated with squamous cell cancer, whereas tight junctions, microvilli, and acinar spaces are associated with adenocarcinoma. Premelanosomes are associated with melanoma, and neurosecretory granules are associated with small cell or neuroendocrine tumors. Lymphoma is typically characterized by an absence of junctions between the cells on electron microscopy. Electron microscopy can be time consuming and expensive; thus, with the availability of immunohistochemical stains, electron microscopy is rarely used.

Immunohistochemical Analysis

Immunohistochemical analyses have become a routine addition to light

microscopy, and a broad range of immunohistochemical markers are used to assist in the diagnosis after light microscopy. Common markers used for adenocarcinomas include thyroid transcription factor (TTF-1) and cytokeratins (CKs) 7 and 20. TTF-1, a nuclear protein, can be positive in lung and thyroid cancers. About 65% to 70% of lung adenocarcinomas and 25% of squamous cell lung cancers stain positive for TTF-1, and, in patients with CUP, this test is helpful in differentiating between a primary lung tumor and metastatic adenocarcinoma (e.g., in patients presenting with metastatic pleural effusion). The CK marker combination pattern depicted in Table 22.2 is also helpful.

Breast markers including estrogen receptor (ER), progesterone receptor (PR), Her-2/neu, and gross cystic disease fibrous protein should be checked in women who present with adenocarcinoma, especially isolated axillary adenopathy. Hep-par-1, a hepatocellular carcinoma marker, aids in the diagnosis of hepatocellular cancer, and CK-19 is sometimes used for cholangiocarcinoma. It can be difficult to distinguish metastatic cholangiocarcinoma, metastatic adenocarcinoma, and hepatocellular carcinoma in patients who present with liver-only metastatic disease. Other markers used in a directed fashion on the basis of past microscopy results include prostatic acid phosphatase and PSA for prostate cancer, and neuron-specific enolase and chromogranin for neuroendocrine cancers. Germ cell tumors often stain for β-hCG and AFP.

TABLE 22.2 Approach to Immunohistochemical Markers Used in Cancer of Unknown Primary Site

CK7	CK20	Primary Tumor
+	+	Urothelial tumors, ovarian mucinous adenocarcinoma, pancreatic adenocarcinoma, and cholangiocarcinoma
+	−	Lung adenocarcinoma, breast carcinoma, thyroid carcinoma, endometrial carcinoma, cervical carcinoma, salivary gland carcinoma, cholangiocarcinoma, pancreatic carcinoma
−	+	Colorectal carcinoma, Merkel cell carcinoma
−	−	Hepatocellular carcinoma, renal cell carcinoma, prostate carcinoma, squamous cell and small-cell lung carcinoma, head and neck carcinoma

TABLE

22.3 Clinical Role of Selected Immunohistochemical Markers

Breast	ER/PR, GCDFP-15, Mammaglobin, Her-2/neu
Lung	TTF-1, Napsin-1A
Mullerian, ovarian	ER/PR, WT-1, PAX-8
Neuroendocrine	Chromogranin, synaptophysin, CD56, NSE
Germ cell	β-hCG, AFP, OCT3/4, CKIT, CD30 (embryonal), PLAP
Urothelial	CK7, CK20, thrombomodulin, uroplakin III
Kidney	RCC, CD10
Hepatocellular	Hep-par-1
Colorectal	CK7, CK20, CDX-2, CEA, Villin
Sarcoma	Desmin1, factor VIII2, CD31, smooth muscle actin for leiomyosarcoma, MyoD1 for rhabdomyosarcoma
Melanoma	S100, vimentin, HMB-45, tyrosinase, and melan-A
Lymphoma	LCA, CD3, CD4, CD5, CD20, CD45
Thyroid	TTF-1, thyroglobulin
Prostate	PSA, PAP
Adrenocortical, sex cord-stromal	Melan-A, inhibin, calretin
Mesothelioma	Mesothelin, calretin, D2-40

ER, estrogen receptor; GCDFP-15, gross cystic disease fibrous protein-15; TTF-1, thyroid transcription factor; SP-A1, surfactant protein A precursor; NSE, neuron-specific enolase; β-hCG, β-human chorionic gonadotropin; AFP, alpha-fetoprotein; PLAP, placental alkaline phosphatase; CEA, carcinoembryonic antigen; LCA, leukocyte common antigen; PSA, prostate-specific antigen; PAP, prostate-specific acid phosphatase.

No single immunohistochemical marker is 100% specific, and many of these tests (as well as serum markers) can be confusing and discordant with radiology and rarely help in the search for a primary tumor or in treatment planning. Although, when used in groups, certain patterns of IHC markers do increase sensitivity and specificity of the diagnosis in the right cellular context (e.g., CDX-2 (+), CK20 (+), and CK7 (−) are highly suggestive of a colorectal cancer profile in a patient presenting with carcinomatosis). Currently, cytogenetics is rarely used in CUP diagnosis.

Serum Tumor Markers

Unfortunately, patients with CUP typically have nonspecific overexpression of many serum tumor markers, including β-hCG, AFP, CEA, CA 125, CA 19-9, and CA 15-3. In patients who present with an undifferentiated carcinoma or a poorly differentiated carcinoma (especially with a midline tumor), β-hCG and AFP should be tested to rule out occult germ-line cancers. None of these markers has been found to have adequate

specificity or sensitivity to consistently identify a primary tumor, nor the predictive value for either response to chemotherapy or survival. Table 22.3 lists several common tumor markers and their roles in clinical evaluation of patients with CUP.

ROLE OF TISSUE OF ORIGIN MOLECULAR PROFILING ASSAYS

The accurate diagnosis of the primary site in CUP would impact patients' prognosis and management, allowing selection of therapies directed toward malignancies from the tissue of origin. Molecular profiling of tumors offers the chance of a systematic human cancer classification and is a technique to improve the putative site of origin diagnosis in CUP patients. Molecular tests that identify molecular signatures of the tissue of origin are commercially available to classify CUP cancers.

Several studies have demonstrated the feasibility of using gene expression profiling with DNA microarray analysis to classify uncertain tumors according to their tissue of origin, by identifying gene subsets whose expression typifies each cancer class. These studies achieved accuracy in identifying the tissue of origin in 78% to 89% of tumors. Furthermore, it has been demonstrated that the patterns of gene expression remain consistent with the tissue of origin and are maintained in distant metastases, even if the metastases develop after a long interval; therefore, it is theoretically possible to build a comprehensive gene expression database spanning a majority of tumor types and use it as a clinical diagnostic tool.

DNA microarray platforms and the quantitative reverse transcription real-time PCR assays (qRT-PCR) use messenger RNA (mRNA) extracted from fresh frozen or formalin-fixed paraffin-embedded (FFPE) tumor tissue that is purified, amplified, and tagged with fluorescent stains. Subsequently, it is hybridized to a DNA microarray consisting of hundreds or thousands of individual gene-specific probes complementary to multiple gene sequences. Relative levels of gene expression in the samples are estimated by measuring the fluorescence intensity for each probe. This kind of strategy can be used for the management of CUP by means of comparison of the multigene expression pattern of a CUP and assignment of the CUP specimen to the primary tumor type, which the CUP molecular signature most closely resembles. In the clinic, real-time quantitative polymerase chain reaction (RT-PCR) is the "gold standard" for gene

expression analysis. However, RT-PCR has a much lower capacity in measuring, at most, a few hundred genes from FFPE tissues and may be of lower quality than that obtained from frozen tissue; formalin fixation can cause formation of cross-links between proteins or between proteins and nucleic acids, which causes lower-purity RNA when compared with frozen tissues.

Several retrospective and prospective studies have evaluated the role of the commercially available assays in the CUP setting. The prospective study by Hainsworth et al., evaluated 289 CUP patients. Of these, 252 had successful assays performed, and 247 (98%) had a tissue of origin predicted. Sites most commonly predicted were biliary (18%), urothelial (11%), colorectal (10%), and non–small-cell lung (7%). Of the 194 patients who received site-directed therapy, the median survival time was 12.5 months (95% CI, 9.1 to 15.4 months).

The routine use of a gene expression profile tool in the diagnosis and management of unknown primary cancer still has limitations. Since a primary cancer is not available, accuracy of the test cannot be easily determined. In addition, there may be genomic differences that exist between a CUP cancer and the solid known primary tumor counterpart with differences in therapeutic outcomes. These possibilities yield questions regarding the clinical impact of determining tissue of origin and performing mutational analysis of metastatic disease in CUP.

At this time, although a microarray-based gene expression profiling test will not obviate the need for thorough clinical investigation, it may facilitate in select patients, more focused testing, especially in those with poorly differentiated carcinomas with nonspecific immunohistochemical profiles. Prospective trials are warranted, especially in the era of NGS.

MUTATIONAL PROFILING: ROLE OF NEXT-GENERATION SEQUENCING IN CUP

As with known cancers, the benefit of NGS for all-comers with CUP is currently poorly defined. Ross and colleagues presented data on 125 CUP adenocarcinomas and 75 CUP without features of adenocarcinoma. They concluded that at least one genomic alteration (GA) was found in 192 (96%) CUP specimens, with a mean (SD) of 4.2 (2.8) GAs per tumor. The top five most frequent mutations reported were in TP53 (110 [55%]), KRAS (40 [20%]), CDKN2A (37 [19%]), MYC (23 [12%]), and ARID1A (21 [11%]). The current controversy is whether cellular context and tissue

classification matter if actionable mutations are identified. The truth may lie somewhere in the middle and is dependent on the site of disease and overall clinicopathologic data. More prospective studies are warranted to define the clinical impact of NGS in CUP cancers (i.e., effect on therapy planning, survival, and quality of life).

SPECIFIC DISEASE SITES

Metastatic Cancer to Cervical Lymph Nodes

Enlarged cervical lymph nodes are often found on biopsy to be positive for metastatic cancer. Patients with squamous cell cancer metastatic to cervical lymph nodes and an unknown primary tumor site have a better prognosis than do patients with CUP overall.

The neck comprises more than 25 nodal basins. These nodes have been grouped into six specific categories to standardize the pathologic evaluation of patients. The classification of cervical lymph nodes is shown in Table 22.4. The most common site of metastasis in patients with head and neck squamous cell cancer is the jugulodigastric or level II upper internal jugular chain nodes, followed by the midjugular or level III nodes. Metastasis to the other cervical nodal groups occurs with less frequency. In those patients with cervical lymph nodes from an occult squamous cell primary tumor, a careful head and neck examination is essential. Adequate lighting and mirrors must be used to visualize the entire oropharynx, hypopharynx, nasopharynx, and larynx. A CT scan of the head and neck (often including CT chest) is indicated to determine the primary tumor site and obtain complete staging information. As mentioned earlier in the text, some of these patients are also candidates for a PET/CT scan.

If no primary tumor is found on physical examination and PET/PET-CT imaging study, panendoscopy is a common next step. This is normally performed in the operating room with the patient under general anesthesia. Esophagoscopy, laryngoscopy, bronchoscopy, and nasopharyngoscopy are performed in an attempt to visualize the region and obtain biopsy specimens from the most common sites of occult squamous cell cancer in the head and neck region. Random biopsies of the most probable tumor site locations are performed on the basis of the location of the adenopathy. Typical occult primary tumor sites in squamous cell cancer are the nasopharynx, the midbase of the tongue, the pyriform sinus, and the tonsils. Table 22.4 shows the common pattern of cervical metastasis from

different squamous cell tumors in the head and neck region. On the basis of the location of the nodal metastases, extrapolation of the likely source of the occult primary tumor is often possible, and the endoscopic examination should be focused on these locations. Bilateral tonsillectomy is an important part of the staging and evaluation process, as it is not rare to see a small primary cancer hidden in the deep crypts of the tonsils.

TABLE 22.4 Classification of Cervical Lymph Nodes and Corresponding Probable Sites of Primary Tumors

Level	Nodes	Primary Tumor Site
I	Submental and submandibular	Floor of the mouth, lips, or anterior tongue; Retromolar trigone or glossopalatine pillar
II	Upper internal jugular chain	Hypopharynx, base of the tongue, tonsils, nasopharynx, or larynx
III	Middle internal jugular chain	Thyroid, hypopharynx, or nasopharynx
IV	Lower internal jugular chain	Lung (40%), thyroid (20%), GI (12%) or GU (8%); and nasopharynx
V	Supraclavicular and posterior triangle	Thyroid, hypopharynx, or nasopharynx
VI	Tracheoesophageal groove	

If the primary tumor site cannot be identified on endoscopy, the standard approach is a combination of radical neck dissection and postoperative radiation therapy. The role of chemotherapy depends on the presence of bulky nodes (N3 disease), and neoadjuvant chemotherapy has not been well studied. On the basis of large series, the expected 5-year survival in these patients is 32% to 55%, and the overall rate of local control is 75% to 85%. Patients with extranodal extension or lymph nodes >6 cm (N3 disease) have higher rates of both local recurrence and distant metastases.

Patients with metastatic adenocarcinoma in cervical lymph nodes from an occult primary tumor have a less favorable outcome than do those with squamous cell cancer. Retrospective series have shown that lymphadenectomy and radiation therapy are much less effective in adenocarcinoma than in squamous cell carcinoma; the rate of local recurrence in these cases is nearly 100%, and the 5-year survival rate is 0% to 10%.

Of particular interest is the presence of an enlarged Virchow

(supraclavicular) node, common in patients with metastatic adenocarcinoma. One study retrospectively reviewed 152 FNA biopsy samples of supraclavicular lymph nodes, comparing the sites of primary tumor when the metastasis was in the right versus the left supraclavicular node. Sixteen of 19 primary pelvic tumors metastasized to the left supraclavicular node, and all (6 of 6) primary abdominal malignancies metastasized to the left supraclavicular node. However, thoracic, breast, and head and neck malignancies did not differ in patterns of metastasis to the right and left supraclavicular nodes. On the basis of this information, the search for the primary tumor should be focused on the abdomen and pelvis in patients who present with adenocarcinoma in a left-sided Virchow node. Front-line chemotherapy based on clinicopathologic presentation is often the treatment of choice in these patients especially given concern for aggressive biology. In patients with cervical adenocarcinoma and isolated or indolent disease, locoregional options including surgery or radiation can be considered after a course of chemotherapy, although there are no prospective trials.

Metastatic Cancer Isolated to Axillary Lymph Nodes

The histologic study of the tumor should be used to guide the evaluation of patients with cancer metastatic to axillary lymph nodes. Patients with squamous cell cancer metastatic to the axillary lymph nodes should undergo a careful skin examination; a thorough head and neck examination; and CT scans of the head, neck, and the chest to look for an occult squamous cell primary tumor.

Men with adenocarcinoma metastatic to an axillary lymph node and CUP should be evaluated for lung, gastrointestinal, and genitourinary primary tumors. Women with adenocarcinoma metastatic to the axillary lymph nodes should be evaluated similarly, although in women the concern for an occult breast primary tumor is high. Women with occult breast cancer who present with axillary metastases constitute approximately 0.32% of all women with breast cancer. When many such patients are treated for a presumptive diagnosis of breast cancer, the recurrence and survival results are similar to those of patients with a similar stage of breast cancer and a known primary tumor. A retrospective review of the mastectomy specimens from patients with occult primary tumors showed that, in 50% to 65% of cases, the primary tumor was ultimately identified in the surgical specimen. Every woman should

undergo a mammogram followed by breast sonography if the mammogram is negative (especially in younger patients with dense breasts). As discussed earlier, MRI of the breast is indicated in women who present with axillary adenopathy and CUP, when mammogram and sonographic findings are negative.

The biopsy specimen from the lymph node should be subjected to routine histologic and immunohistochemical evaluation for ER, PR, and Her-2/neu. Additionally, other breast markers including GATA-3 and mammoglobin are also performed. Although neither highly sensitive nor highly specific, the presence of ER or PR in this clinical scenario strongly suggests a breast primary tumor.

The treatment for women with adenocarcinoma metastatic to axillary lymph nodes has evolved dramatically over the last decade. The three general approaches are immediate mastectomy, observation, and radiation therapy. Immediate mastectomy is not performed in most patients if the imaging studies are negative because the chances of finding a primary are low. Observation with axillary dissection can result in recurrence in the breast (25% to 75%, depending on the study), requiring further therapy. The third approach is breast-conservation therapy with locoregional radiation therapy, which has been shown to decrease the local recurrence rate and is the preferred approach for most patients at the MD Anderson Cancer Center. Our results show that in patients who have undergone axillary lymph node dissection alone, the incidence of local recurrence is 65% at 10 years, whereas a combination of axillary lymph node dissection and radiation therapy reduces the local recurrence rate to 25%. With this treatment, the overall survival rate was no different from that of patients with the same nodal stage of disease who had undergone mastectomy. The addition of adjuvant chemotherapy to surgery and radiation therapy increased the survival rate from 60% to 85% at 10 years. Tamoxifen should be part of the therapy for women of any age whose primary tumor (if identified) or axillary nodal metastases express ER or PR.

A retrospective study at the MD Anderson Cancer Center included 45 women with isolated axillary nodal metastases without a known primary tumor. The median follow-up duration was 7 years. Patients underwent either mastectomy or breast-conservation therapy; external beam radiation therapy was used in 71% of patients, and systemic chemotherapy was used in 73%. No significant difference was found between mastectomy and breast conservation in locoregional recurrence, distant metastases, or 5-

year survival rate. Regardless of the surgical treatment used, the number of involved nodes was the only determinant of survival.

Cancer Metastatic to the Inguinal Nodes From an Unknown Primary Site

A relatively infrequent presentation of metastatic CUP is metastases to the inguinal lymph nodes. Excluding melanoma, the two most common histologic types are unclassified carcinoma and squamous cell carcinoma. Adenocarcinoma is rarely observed. In evaluating patients with inguinal metastases, a thorough investigation for the primary tumor should include examination of the skin of the lower extremities, perineum, buttocks, anal canal, and pelvic region. If the inguinal node is the solitary area of presentation, excision followed by local radiation therapy is the next preferred step. For bulky bilateral adenopathy, neoadjuvant chemotherapy followed by surgery (inguinal lymph node dissection) and radiation therapy can also be considered if there are no other sites of metastatic disease. These patients are prone to lymphedema after multimodality therapy, so they should be educated regarding the risks and undergo treatment if lymphedema develops.

Peritoneal Carcinomatosis of Unknown Primary Site

Patients with peritoneal carcinomatosis of unknown primary site can present with ascites, bowel obstruction, or nonspecific gastrointestinal symptoms. The two subgroups in this category include (a) patients with mucin-producing adenocarcinoma with and without signet ring cells and (b) women with primary peritoneal carcinomatosis. Patients with mucin-producing adenocarcinoma often have multiple peritoneal implants, with the primary site most likely being the gastrointestinal tract (i.e., stomach, small bowel, appendix, or colon). Patients in this group have a poorer prognosis and respond poorly to currently available treatment regimens. These patients should undergo an upper endoscopy and colonoscopy to evaluate for a gastrointestinal primary tumor. If immunohistochemical analysis shows a CK 20+, CK7−, CDX2+ pattern—a potential colon cancer profile—a colon cancer–based treatment regimen is often considered even in the absence of a colon primary tumor.

The second subset is composed of women with primary peritoneal carcinomatosis. A histopathologic analysis of these patients reveals cells

with serous papillary features and, on occasion, psammoma bodies. These patients may have elevated CA 125 levels but do not have obvious ovarian cancer (negative results on CT pelvis and transvaginal sonography). Several studies have found that women who present with peritoneal carcinomatosis should be treated in a similar fashion to those with known advanced ovarian cancer, including maximal surgical cytoreduction at initial laparotomy followed by platinum-based combination chemotherapy. One study found a prolonged median survival of 13 months in patients who had undergone paclitaxel- and carboplatin-based chemotherapy, and 25% of the patients had progression-free survival of more than 2 years.

Unknown Primary Tumor With Metastatic Liver Disease

The surgeon is occasionally involved in the evaluation of patients who present with metastatic disease to the liver from an unknown primary tumor. The liver tumor may be discovered when the patient presents with symptoms on routine physical examination or incidentally on a radiologic study such as an abdominal sonogram or CT scan.

When patients present with metastatic disease to the liver and CUP, the most common cell type is adenocarcinoma (approximately 60% to 65%). However, anaplastic or poorly differentiated carcinoma, small-cell carcinoma, squamous cell carcinoma, neuroendocrine cancer, and unclassified tumors are also found. Most patients undergo a CT scan of the chest, abdomen, and pelvis; mammogram (in women); and an upper endoscopy and colonoscopy if suggested by marker data or symptoms. The overall survival of these patients is usually poor (median, 7 months), although a survival benefit (approximately 12 months) can be seen in patients who have a good performance status and respond to chemotherapy. It is important to note that incidence of cholangiocarcinoma has increased in the last 5 years, partially due to better identification of these cancers that were previously labeled as CUP.

A subgroup of patients who present with CUP and liver metastases have low-grade neuroendocrine carcinoma. These may be diagnosed incidentally or when patients complain of hormonal symptoms (diarrhea, flushing, or nausea) or pain. Low-grade neuroendocrine cancers can remain indolent for several years with slow progression and may not need treatment for a long time (hormonal or other). Tumor markers, including serum chromogranin, neuron-specific enolase, and urine 5-HIAA, may be elevated. If a patient has carcinoid symptoms, endocrine therapy alone for

hormone-related symptoms with somatostatin analogs should be used. Specific local therapies, such as right hepatectomy or chemoembolization, or systemic therapies, such as chemotherapy or more recently developed targeted therapy (antiangiogenic agents and mTOR inhibitors) are indicated: (1) if the patient has bulky disease or progression or (2) if the patient is symptomatic with pain or uncontrolled endocrine symptoms. Sunitinib and Everolimus are FDA-approved front-line therapies for low-grade neuroendocrine cancers.

Role of the Surgeon in Cancer of Unknown Primary Site

Surgeons interact with patients with CUP at all stages in their treatment from diagnosis to palliation. Frequently, the amount of tissue necessary to complete IHC, cytogenetic, and molecular profiling studies on a percutaneously obtained specimen exceeds the amount tissue available through this method of biopsy. Surgeons are often asked to assist with diagnosis by performing excisional biopsy, such as for lymphadenopathy to evaluate for lymphoma or for CUP which requires adequate tissue to perform all essential diagnostic investigations. Patients with CUP with a single site of disease and no evidence of distant metastases may be candidates for a potentially curative resection. Determining to which patient and at what time to offer surgery to a patient with CUP is challenging. Factors influencing this determination include the biology of the tumor, including disease-free interval; the tissue of origin (if able to be identified) and the typical behavior of a poorly differentiated cancer of that tissue type; response to neoadjuvant chemotherapy or immunotherapy; the performance status of that patient; and lastly, the effect on the patient's quality of life following surgery.

Chemotherapy for Metastatic Cancer of Unknown Primary Site

Data from CUP trials are difficult to interpret because patients with CUP are a heterogeneous group. When chemotherapy is given to unselected groups of patients with metastatic CUP, an overall 5% to 10% 5-year survival rate can be anticipated, with median survival in most studies between 6 and 13 months. Patients with favorable subtypes (e.g., peritoneal carcinomatosis or lymph node–predominant disease) benefit from chemotherapy. Traditionally, cisplatin-based combination

chemotherapy regimens have been used to treat patients with CUP. In a phase II study by Hainsworth et al., 55 patients with CUP were treated with paclitaxel, carboplatin, and oral etoposide every 21 days. Most were previously untreated, with only four having undergone previous chemotherapy. The overall response rate was 47%, the median overall survival was 13.4 months, and the regimen was well tolerated. Briasoulis et al. found comparable response rates and median overall survival in 77 patients with CUP with paclitaxel and carboplatin and without oral etoposide. In this study, patients with nodal or pleural disease and women with peritoneal carcinomatosis had a better response rate and an overall survival of 13 and 15 months, respectively. A phase II randomized trial by Culine et al. (the French Study Group on Carcinomas of Unknown Primary 01) studied 80 patients who were randomly assigned to receive either gemcitabine + cisplatin (GC) or irinotecan + cisplatin (IC). Seventy-eight patients were assessable for efficacy and toxicity. Objective responses were observed in 21 patients (55%) in the GC arm and in 15 patients (38%) in the IC arm. The median survival was 8 and 6 months in the GC and IC arms, respectively (median follow-up of 22 months).

Patients with poorly differentiated carcinoma, the possible germ cell equivalents, have traditionally undergone a trial of a cisplatin-based regimen. Patients with squamous cell cancer or neuroendocrine cancer have a significantly better response to chemotherapeutic agents than do patients with other tumor types. The role of second-line chemotherapy in CUP is poorly defined. In the current era, therapies are chosen based on clues from presentation, immunohistochemistry, and response to first-line therapy.

Immunotherapy is quickly moving to the forefront in the treatment of patients with locoregional disease and distant metastatic disease in many cancer types, such as melanoma, and will likely have future implications for the treatment of CUP. Currently, there are limited indications for immunotherapies in CUP. However, checkpoint inhibitors have been utilized in multiple phase II trials to evaluate their efficacy in patients with metastatic disease of known primary sites, such as colorectal cancer and squamous cell cancer of the head and neck. Notably, Le et al. demonstrated clinical benefit of the checkpoint inhibitor pembrolizumab in a small phase II trial that included patients with mismatch-repair deficiency regardless of colorectal origin, with immune-related progression-free survival rate of 78%. Whether checkpoint inhibitors can

be used in CUP cancers with MSI-high presentations or viral-induced pathogenesis (e.g., HPV-positive inguinal nodal disease) remains to be seen.

Although cure is an unrealistic goal for many patients with CUP, surgeons often are involved in the palliative care of such patients and, in some selected cases, are involved in planning definitive therapies for patients with locoregional disease. CUP is the epitome of personalized medicine, and patients should be managed by a multidisciplinary team to ensure improved survival and quality of life.

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23 Surgical Emergencies in Cancer Patients

Brian D. Badgwell

Oncologic emergencies have been defined as “an acute condition that is caused by cancer or the treatment of cancer and that requires intervention as soon as possible to avoid mortality or severe permanent morbidity.” Cancer patients are at increased risk of emergent conditions due to malnutrition, immunosuppression, limited physiologic reserve, and side effects of treatment. In addition, despite the increasing use of targeted therapy and improvements in managing side effects of systemic therapy, treatment can create oncologic emergencies. Tumors can also create emergent conditions through local or systemic effects.

Surgical consultation for oncologic emergencies generally represents a complex clinical scenario requiring a rapid gathering of information of the patients’ previous treatment and oncologic history and at least an attempt at multidisciplinary input. Such situations require physician to physician interaction and unfortunately often occur in the middle of the night or emergency room, when the primary oncology or treatment team is not available. Surgeons should not hesitate to contact the “off-service” physician that may be best informed of the patients’ treatment history and current prognosis. Patients must be assessed quickly to determine if they are stable or unstable. A quick assessment, similar to the Advanced Trauma Life Support evaluation of trauma patients, can be utilized to evaluate the airway, vital signs, and neurologic status.

For the purposes of this chapter the spectrum of oncologic emergencies will be categorized into surgical and medical, with emphasis on the surgical emergencies and particularly on intra-abdominal conditions. As almost half of all cancers diagnosed are not amenable to cure; the distinction between oncologic emergencies and palliative care is sometimes difficult to distinguish. Therefore, this chapter will also include a summary on emergent palliative surgical consultations.

SURGICAL ONCOLOGIC EMERGENCIES

Bowel Obstruction

Bowel obstruction is a frequent cause for general surgical evaluation and cancer patients are no exception. As many cancer patients have had previous intra-abdominal surgery, bowel obstruction can be due to adhesions or associated with hernias. Such patients are treated according to commonly accepted surgical principles. In patients with a history of cancer, however, it can be difficult to determine if the cause of obstruction is due to adhesion formation or represents a malignant bowel obstruction.

The general approach to a patient with a bowel obstruction is to obtain a history with focus on determining the type of obstruction and whether the obstruction represents a partial versus complete obstruction. Obstructions can be classified according to location such as gastric outlet obstruction (GOO), small bowel obstruction (SBO), or large bowel obstruction (LBO). Obstructions may be classified according to the degree of obstruction such as a partial, complete, or closed loop. Furthermore, obstruction etiology may be included such as mechanical (adhesive, hernia, malignant, or intrinsic/extrinsic compression) or nonmechanical (pseudo-obstruction). Recent chemotherapy and treatment history, as always, is of critical importance in evaluating the risk/benefit ratio of surgical intervention. Physical examination should start with the hemodynamic status of the patient. The abdominal examination is performed to determine the severity of obstruction, the possibility of underlying strangulation, and the presence of hernias. During the evaluation, the need for a nasogastric tube, Foley catheter, and aggressive intravenous fluid resuscitation should be addressed and can be influenced by laboratory findings. The goal of management should be to perform surgical intervention prior to the development of bowel ischemia, however, physical examination findings of fever, tachycardia, and leukocytosis can suggest the presence of ischemia or even perforation. Initial imaging typically is an acute abdominal series (chest, supine abdomen, and upright abdomen plain films) to evaluate for intraperitoneal air and to help determine the cause and severity of the obstruction. CT imaging can be a useful adjunct in determining etiology, severity, and site of obstruction. A gastrografin enema or sigmoidoscopy may be required to rule out distal obstruction.

Malignant Bowel Obstruction

Malignant bowel obstruction is defined as “the blockage of the small or large intestine in a patient with advanced cancer.” Although it is understood that this definition applies to blockage caused by tumor, in many patients it is not evident on imaging if the obstruction is due to direct tumor involvement. Bowel obstruction in patients with a history of cancer may be due to benign causes in up to a third of patients. Regardless of the cause, indicators of adverse outcome present at the time of initial evaluation upon which to base treatment decisions have not been firmly established. There is a paucity of prospective research and no evidence-based algorithms upon which to base treatment decisions for malignant bowel obstruction. Much of the treatment is based upon retrospective reviews that outline the considerable morbidity and mortality associated with surgery for malignant bowel obstruction. As outlined in a review by Ripamonti et al., the operative mortality for surgery ranges from 9% to 40% with morbidity rates of 9% to 90%, with very little improvement even in the more recent reports.

Malignant bowel obstruction rarely requires urgent and immediate operative intervention, which allows time for an appropriate evaluation and imaging. CT scanning can be very helpful in identifying factors associated with diminished outcome in surgery for malignant bowel obstruction, such as carcinomatosis and ascites. Advanced age, hypoalbuminemia, and diminished performance status are also felt to represent adverse predictors of outcome. Although it is difficult to delineate absolute contraindications to surgery for malignant bowel obstruction, areas of significant concern include previous abdominal surgery which showed diffuse metastatic cancer, intra-abdominal carcinomatosis, imaging suggesting a motility disorder, ascites which rapidly recurs after drainage, extra-abdominal metastases which cause symptoms that are difficult to control, and previous radiotherapy to the abdomen/pelvis. The combined findings of carcinomatosis and ascites are notable in that surgery is rarely successful and the risk of postoperative morbidity is considerable. Patients felt to not be candidates for surgery may benefit from corticosteroids, antiemetics, octreotide, analgesics, or venting gastrostomy tubes.

Gastric Outlet Obstruction

With reported mortality rates of up to 30% for palliative gastrojejunostomy in patients with malignant GOO, patients should be selected carefully and

considered for endoscopic stent placement, although this option is heavily dependent on local availability and experience. Limited data from randomized trials and observational or retrospective studies comparing stent placement to gastrojejunostomy demonstrate a decreased length of stay and time to toleration of liquid diet with stent placement but an increased rate of recurrent obstructive symptoms. Some authors have recommended attempting stent placement in patients with a relatively short life expectancy and pursuing gastrojejunostomy in those with a longer life expectancy.

TABLE 23.1 Treatment Strategies for Patients With Gastrointestinal Obstruction, Stratified by Site of Obstruction

Treatment	GOO (%)	SBO (%)	LBO (%)
Surgery	44	25	57
Procedures[a]	34	24	18
Medical only[b]	22	52	25

[a]Endoscopy or interventional radiology procedures.
[b]Nonoperative and nonprocedural treatment.
GOO, gastric outlet obstruction; SBO, small bowel obstruction; LBO, large bowel obstruction.

Small Bowel Obstruction

Small bowel is the most frequent site of obstruction, representing two-thirds of all malignant bowel obstructions, although in approximately 20% of cases both small and large bowel are involved. Surgery remains an important consideration in these patients as stents are difficult to place outside of the proximal small bowel. Surgery may involve a bypass procedure or resection. Determining the need for operation can be difficult as not all partial bowel obstructions in patients with a history of cancer are due to direct tumor involvement and also partial obstructions may resolve with conservative therapy.

Large Bowel Obstruction

A significant advancement in the treatment of malignant LBO has been endoscopic self-expandable metallic stents. A recent systematic review found that although the evidence-based quality of the studies was generally low, expandable stents demonstrated a lower rate of serious adverse events and hospital stay with similar mortality to open surgery (Watt et al.).

A recent review of patients with advanced cancer and gastrointestinal obstruction at MD Anderson reported a median overall survival of 3.5 months, highlighting the need for careful patient selection to identify patients that will experience symptom improvement from surgery and recover back to meaningful quality of life prior to death from disease progression (Badgwell et al.). Table 23.1 demonstrates the treatment strategies for this group of patients, stratified by anatomic site of location: GOO, SBO, and LBO. Venting gastrostomy tubes can be a possibility for patients with limited surgical options, allowing for nasogastric tube removal and discharge home with hospice. In this series, 24% of patients with GOO, 23% with SBO, and 8% with LBO were treated with venting gastrostomy tube placement. Rather than an algorithmic approach, patients with malignant bowel obstruction require a multifaceted approach that incorporates the many variables important in treatment selection, as illustrated in Figure 23.1.

Bowel Perforation

Cancer patients may be at increased risk of bowel perforation due to side effects of chemotherapy or radiation, immunosuppression, steroid administration, or direct tumor invasion. Cancer patients may experience iatrogenic bowel perforation as they are frequently subjected to endoscopic and interventional procedures. Bowel perforation may be caused by conditions unrelated to oncologic disease or treatment such as diverticulitis, peptic ulcer disease, or appendicitis. Outside of any recent treatment or oncologic issues these patients are usually treated with prompt surgical intervention, although nonoperative management of diverticulitis with a contained abscess or perforation may be appropriate.

The majority of cancer patients with bowel perforation will have advanced or incurable cancer. Therefore, in addition to clinical presentation, factors such as prognosis, symptom burden, treatment history, and patient and family desires play an equally important part in management. Although the majority of patients will be managed with surgery, comfort care and nonoperative management are options in this complex clinical scenario.

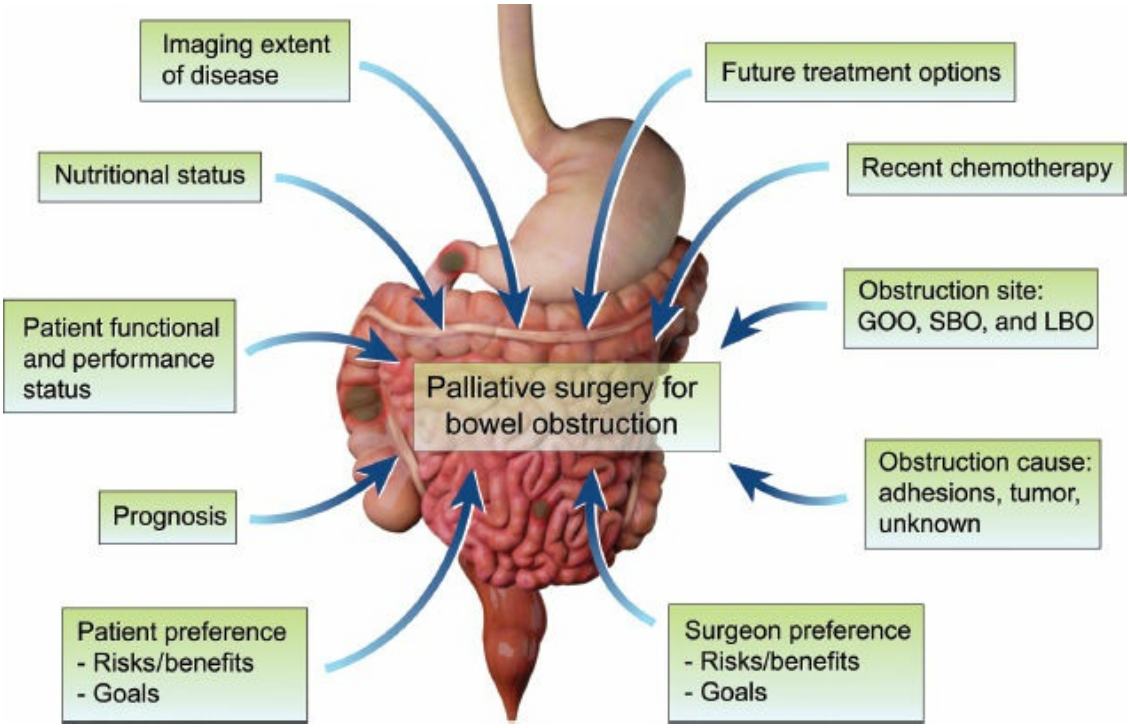

Figure 23.1 Multifaceted approach required in the evaluation of patients with malignant bowel obstruction.

Approximately 2% of colorectal cancers will present with perforation. Perforation may occur as a direct result from transmural invasion of the bowel wall or, less frequently, as a result of distal obstruction leading to proximal bowel dilation and perforation. Perforated colorectal cancers have been associated with both increased local and systemic recurrence. Operative mortality rates are also increased and can approach 20%.

A chemotherapy-associated bowel perforation that deserves note is bowel perforation in association with bevacizumab. Bevacizumab, a humanized monoclonal antibody to vascular endothelial cell growth factor, has demonstrated efficacy in combination with chemotherapy for patients with metastatic colorectal cancer and lung cancer and therefore is being studied and utilized for a wide variety of malignancies. The incidence of bowel perforation in patients receiving bevacizumab is 1% to 2%, although it appears to vary across cancer types. Although infrequent, bevacizumab-associated bowel perforation is associated with a 30-day mortality rate of 13% to 50%. Concerns regarding emergency surgery in the setting of recent bevacizumab administration include wound-healing difficulties and bleeding. The concern over increased postoperative complications is demonstrated in the practice that most surgeons wait for 6 weeks after bevacizumab administration prior to proceeding with elective

surgery. Consideration should be given to the need for stoma placement in patients with bevacizumab-associated bowel perforation requiring operation.

Cholecystitis and Biliary Obstruction

It is unclear if cancer patients receiving systemic therapy are at an increased risk of calculous cholecystitis. Patients with immunosuppression, malnutrition, and those receiving systemic therapy may be at increased risk for acalculous cholecystitis. Other causes for cholecystitis in the cancer population include hepatic embolization and biliary stent placement. Cancer patients may have intra-abdominal fluid or malignant ascites that complicates interpretation of pericholecystic fluid or gallbladder wall thickening on ultrasound or CT imaging. Hepatobiliary scintigraphy may be required to confirm the diagnosis of cholecystitis. Treatment for cancer patients may be atypical in that not all patients can undergo a prompt laparoscopic cholecystectomy due to treatment issues such as recent chemotherapy, immunosuppression, neutropenia, malnutrition, comorbid conditions, and stage of disease or prognosis. With these concerns in mind, some patients are best treated with a cholecystostomy tube to prevent delaying treatment or to perform a surgery that has a risk of conversion to an open procedure that may not be appropriate in the context of the oncologic prognosis. Subsequent laparoscopic cholecystectomy and cholecystostomy tube removal has been described with low conversion rates.

Biliary Obstruction

Patients rarely present with biliary obstruction and cholangitis but treatment in this situation focuses on endoscopic drainage and antibiotics. Stable patients with potentially resectable causes of biliary obstruction are described elsewhere; unresectable patients may benefit from endoscopic, percutaneous, or surgical bypass procedures. In general, endoscopic/percutaneous methods of palliation offer less initial morbidity but decreased durability of palliation. Surgical methods conversely have more up-front morbidity with a longer durability of palliation; the best approach remains a matter of debate and is also dependent on individual institutional capability. Biliary obstruction from metastatic disease present in the porta hepatis can be associated with a wide variety of cancers and often represents a condition with a very poor prognosis and prohibitive

surgical mortality and morbidity. Endoscopic or percutaneous biliary stent placement best accomplishes drainage and therefore subsequent consideration can be given to radiation therapy with or without chemotherapy.

Neutropenia and Abdominal Pain

Neutropenia is a frequent toxic effect of chemotherapy. Abdominal pain in neutropenic patients can represent a wide variety of conditions with significant mortality for which surgeons are frequently asked to evaluate in consultation. Surgeons asked to assist in diagnosing and managing this scenario must consider the broad list of general surgical conditions that can cause abdominal pain, but also conditions unique to the neutropenic patient. Neutropenic enterocolitis is one such entity and has been referred to as neutropenic enteropathy, agranulocytic colitis, or typhlitis (if the disease is confined to the cecum). In a recent series of 60 patients from MD Anderson, neutropenic enterocolitis was found in 28%, SBO in 12%, and the cause remained uncertain in 35% (Badgwell et al.). Less frequent conditions included *Clostridium difficile* colitis, diverticulitis, appendicitis, cholecystitis, colonic pseudo-obstruction, and splenic rupture. Thirty- and 90-day mortality rates for all patients in this series was 30% and 52%, respectively, and likely reflects the significant underlying disease and frequent comorbidities found in this patient population. Surgical intervention was performed in 15% and attempts were made to delay surgery until resolution of neutropenia.

The clinical and pathologic criteria for diagnosing neutropenic enterocolitis have not been firmly established. A commonly accepted clinic diagnostic triad is neutropenia (neutrophil count of <1,000 cells/μL), abdominal pain, and bowel-wall thickening on imaging. In patients with diarrhea, it is important to rule out *C. difficile* colitis. Surgery is reserved for perforation, sepsis, or progression of disease and worsening of the overall condition felt to be attributable to the enterocolitis.

The mortality rate associated with surgery in patients with neutropenia has been well established with early reports documenting mortality rates of 41% to 57%. More recent reports reflect attempts to delay surgery to allow for resolution of neutropenia and demonstrate improved survival rates, which also may be attributable to improved critical care, imaging, antibiotics, colony stimulating factors, and white blood cell transfusions. There are no formal recommendations for medical treatment of

neutropenia and abdominal pain and many clinicians rely on recommendations from the Infectious Diseases Society of America for febrile neutropenia. These guidelines propose either monotherapy with cefepime/ceftazidime/carbapenem/piperacillin–tazobactam or duotherapy with an antipseudomonal β-lactam and an aminoglycoside. However, the majority of patients in our series were treated with Vancomycin for suspicion of gram-positive infection in patients with severe sepsis and metronidazole was often considered as anaerobic species, such as *Clostridium*, are known to be involved in neutropenic enterocolitis. The use of antifungal agents is not established but can be considered in patients that remain febrile or shows signs of infection concomitantly with neutropenia for ≥5 days, again based on recommendations for febrile neutropenia.

Hemorrhage

Gastrointestinal bleeding in cancer patients is most commonly found to arise from benign causes such as peptic ulcer disease and gastritis. Primary tumors as the cause of bleeding are rarely a source of brisk, uncontrollable hemorrhage. Gastric lymphoma patients receiving systemic chemotherapy are a population at high risk of gastrointestinal bleeding with reported rates of up to 11%. Metastatic tumors to the gastrointestinal tract, such as melanoma, can be a frequent source of bleeding but also are more commonly associated with a chronic, relatively slow rate of blood loss. The management approach is that of standard surgical principles. After stabilization in the intensive care unit, initial diagnostic approaches are based on clinical signs indicating an upper or lower gastrointestinal source. Endoscopic control of malignant upper gastrointestinal bleeding has good success rates and often allows for elective surgical intervention. Postoperative mortality rates in patients undergoing surgery for bleeding gastric cancer approaches 10% and therefore consideration should be given to a second endoscopy prior to surgery, based on hemodynamic stability. For signs of lower gastrointestinal bleeding, the initial diagnostic procedure is again endoscopy which can also allow for bleeding control and an elective surgical procedure. Nuclear red blood cell scans and angiography are adjunctive maneuvers.

Anorectal Infections

Anorectal infections in noncancer patients are rarely a source of major morbidity or mortality and are typically treated with prompt incision and drainage. Anorectal infections in patients with cancer receiving systemic therapy, however, can be a significant and potentially lethal condition. Reports from the 1970s describing anorectal infections in immunosuppressed cancer patients documented mortality rates as high as 50%. The authors of these early reports noted that many anorectal infections in the immunosuppressed, cancer population were ulcerative without associated abscess formation and recommended caution in proceeding with surgical intervention. A recent study from the National Cancer Institute, demonstrating a selective surgical approach, found that surgery was required in 37% of patients and there were no deaths associated with anorectal infections (Lehrnbecher et al.). In a recent study from MD Anderson Cancer Center, 100 patients with anorectal infections underwent surgical oncology consultation and 58% were treated with operative intervention (Badgwell et al.). Identification of an abscess and erythema on physical examination were most commonly associated with surgical intervention. The frequency of necrotizing soft tissue infections in this study was low (2%) but was associated with the only infection-related mortality (1%).

Palliative Aspects of Surgical Oncologic Emergencies

The definition of palliative surgery has many minor variations but is generally defined as any procedure that is performed to reduce symptoms or improve quality of life in a patient with an advanced or incurable malignancy. Palliative surgical procedures have been reported to account for 13% of all operations at a major US cancer center and up to 21% of all operations performed by surgical oncologists. A recent report attempted to determine the percentage of inpatients undergoing surgical evaluation at a cancer center that met the criteria for palliative evaluation (Badgwell et al.). Surgical palliative evaluation was defined as a consultation with patients who have symptoms attributable to an advanced or incurable malignancy, including patients who were evaluated for symptoms attributable to complications or toxicity of the treatment of their advanced or incurable malignancy. In this study, 40% of all inpatient surgical oncology evaluations were requested for symptom palliation in patients with advanced or incurable malignancies. Gastrointestinal obstruction was the most common reason for consultation (43%) while wound

complications/infection and gastrointestinal bleeding accounted for 10% and 8%, respectively. Almost half of the patients had received systemic therapy within 6 weeks preceding the request for surgical palliative consultation. Palliative surgical procedures were performed in 27% of patients, with a 90-day morbidity and mortality rate of 40% and 7%. The median overall survival of all patients undergoing palliative surgical evaluation was only 2.9 months, again highlighting the need for careful patient selection.

Palliative surgical consultation is arguably the most complex and time-consuming category of surgical consultation and evaluation. Although the majority of patients deemed suitable for surgery will experience symptom improvement, roughly a quarter of patients will develop recurrent symptoms and another quarter will develop new symptoms requiring evaluation during short-term follow-up. There are many approaches to palliative surgery consultation such as the palliative triangle technique, traditional risk–benefit, and having a set of questions to identify patient's goals and what trade-offs they are willing to make in pursuit of their goals. One example of a risk–benefit-based approach utilized for teaching at our institution is outlined in Figure 23.2. The first step in this approach is to thoroughly review the patient history and previous imaging, in addition to discussing the family dynamics with the assigned nurse prior to entering the room. Next, an empathic statement, such as an apology for meeting the patient in such circumstances, can acknowledge the difficulty that these patients experience in going from a therapeutic to palliative management strategy. When asking about prognosis it is important to not state a prognosis that significantly differs from the patient's understanding of their prognosis. Silence from the physician, during at least a few periods of the consultation can be crucial to allow the patient the opportunity to express their understanding of their symptoms and goals. Several visits may be required to proceed through this approach, particularly in situations where surgical intervention is not an option.

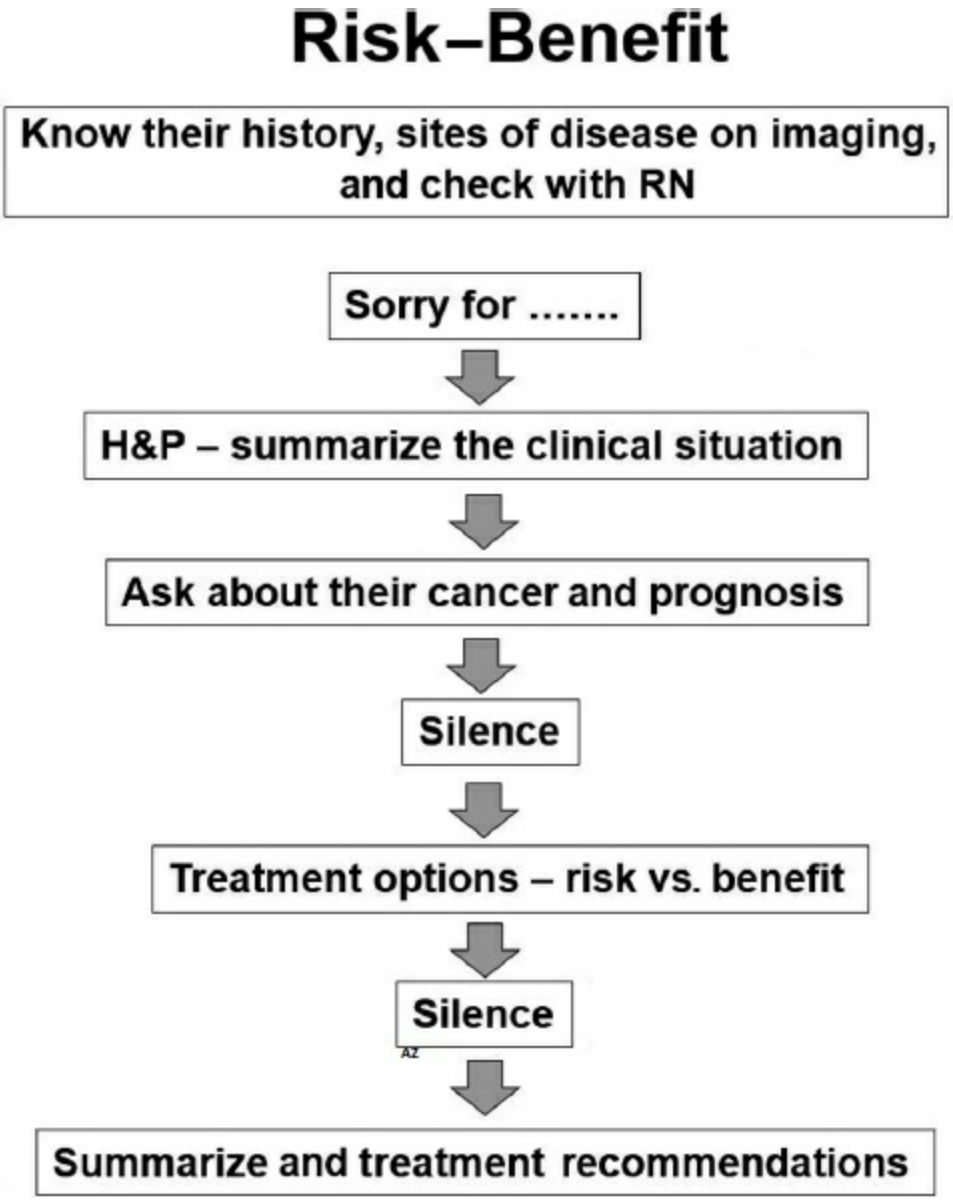

Figure 23.2 Example of a risk–benefit-based approach to palliative surgical consultation.

Future studies are needed to characterize patients with surgical oncologic emergencies requiring inpatient evaluation and identify indicators of adverse surgical outcome based on specific symptom clusters such as malignant bowel obstruction or gastrointestinal hemorrhage. These studies would also be strengthened by inclusion of patient reported outcomes and symptom improvement data, comorbidity indices, performance status, and larger numbers through multi-institutional collaboration.

MEDICAL ONCOLOGIC EMERGENCIES

Superior Vena Cava Syndrome

- Superior vena cava obstruction can result from invasion, fibrosis, thrombosis, or external compression by malignancy.
- Lung cancer (leading cause in 65% to 85%), lymphoma, breast cancer, and thymic cancer are common malignant causes. In the majority of cases, there is time to obtain a histologic diagnosis to guide therapy.
- Clinical presentation is dyspnea, cough, headache, facial/neck/chest wall venous engorgement, cyanosis, worsened when patient bends forward or supine position. Symptoms typically develop slowly and progress over a few weeks.
- CT angiography is the initial test of choice and can differentiate thrombosis from external compression as well as guide imaging-directed biopsy. It can also detect other emergent conditions that may be found such as spinal cord compression, pericardial metastases, and impending airway obstruction.
- Diuretics, head elevation, steroids, intubation, and radiation therapy may be required. Vena caval stents have been described in severe cases as temporizing measures during an ongoing workup.
- Further treatment is tumor-specific therapy or thrombolysis. Removal of any venous catheters is required.

Spinal Cord Compression

- The majority of patients present with back pain that may be exacerbated by movement, recumbency, coughing, sneezing, or straining.
- Progressive symptoms involve weakness, numbness, urinary retention, and constipation.
- MRI is the current study of choice.
- Treatment may involve steroids, radiotherapy, systemic therapy, or surgery.

Pericardial Tamponade

- Signs and symptoms can include chest pain, dyspnea, tachycardia, distant heart sounds, jugular venous distention, pulsus paradoxus, and ultimately hypotension.
- Electrocardiogram demonstrates low voltage. Echocardiography is the most useful test for diagnosing and evaluating the hemodynamic severity of a pericardial effusion.
- Pericardiocentesis can be performed under echocardiographic

monitoring with placement of a drainage catheter and subsequent tetracycline or thiotepa (alkylating antiblastic agent) sclerosis.
- Surgical treatment generally consists of subxiphoid pericardiotomy, however, if a previous subxiphoid approach has been performed a transthoracic pleuropericardial window may be a better option.
- Radiotherapy can also be administered, particularly in patients with malignant effusion secondary to lymphoma.

Paraneoplastic Crises

Hypercalcemia

- Common cancer etiologies include breast, lung, kidney, and multiple myeloma and are often in association with bone metastases.
- Elevated PTH levels in association with hypophosphatemia indicate ectopic PTH secretion.
- Hypercalcemia secondary to malignancy demonstrates elevated or normal serum phosphate.
- EKG changes can be seen with shortening of the QT interval and arrhythmias that can progress to bradycardia, prolonged PR interval, shortened QT interval, and widened T waves.
- Symptomatic patients and those with a serum calcium >12 mg/dL require prompt treatment.
- Intravenous hydration followed by diuretics is the initial treatment.
- Bisphosphonates can reduce bone resorption from metastatic disease but require 3 to 4 weeks to take effect.
- Plicamycin is also an effective inhibitor of bone resorption that can take effect within 6 to 48 hours but has toxicities such as thrombocytopenia, hypotension, and hepatic/renal insufficiency.
- Gallium nitrate is another effective inhibitor of bone resorption with a main side effect of nephrotoxicity.

Hyponatremia/SIADH

- Can result in mental status changes, nausea, headaches, seizures, coma, and ultimately death. Small cell lung cancer is a commonly associated malignancy but may be present with prostate, adrenal, esophagus, pancreas, colon, and head and neck cancers.
- Pseudohyponatremia is due to hyperproteinemia, hyperglycemia, or hyperlipidemia.
- Chemotherapy such as vincristine and cyclophosphamide may be

associated with hyponatremia.

- SIADH findings include a low BUN, hypouricemia, and hypophosphatemia. Treatment for SIADH is tumor and cause specific. For example, small cell lung cancer–associated SIADH may be treated with appropriate chemotherapy while SIADH resulting from brain metastases may improve with the use of corticosteroids and radiation therapy. Treatment otherwise consists of water restriction to 500 to 1,000 mL/day to correct the sodium over several days. Further treatment can involve demeclocycline, an ADH antagonist.
- Severe hyponatremia can be treated with 3% hypertonic saline infusion with IV Lasix, although the rate of correction should be limited to 0.5 to 1.0 mEq/hr to minimize the risk of CNS toxicity.

Hypoglycemia

- Symptoms include weakness, dizziness, and confusion that can progress to seizures and coma.
- There are many noncancer causes but insulinomas, adrenocortical tumors, hepatomas, sarcomas (fibrosarcoma, neurofibrosarcoma, and hemangiopericytoma), and mesotheliomas may produce hypoglycemia.
- Resection is performed, when possible. For unresectable insulin-secreting tumors, diazoxide, radiation, diet modification, corticosteroids, glucagon, and growth hormone may be of benefit.

Tumor Lysis Syndrome

- This syndrome is manifest by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia resulting from rapid cell lysis from cytotoxic therapy. Acute renal failure is caused by renal tubule accumulation of uric acid or calcium phosphate.
- Tumor lysis syndrome most often occurs in lymphoma and leukemia after systemic chemotherapy but may occur in other cancer types following radiation, hormonal, or ablative therapy.
- Preventive measures include IV hydration, alkalinization of the urine, and allopurinol administration.
- Treatment involves correcting the electrolyte abnormalities, particularly hyperkalemia. Hemodialysis may be required.

Central Venous Catheter Sepsis

- IV antibiotic therapy of catheter-based infections has been reported with success rates of up to 80%.

- However, patients may be optimally treated with catheter removal and is indicated for patients with persistent blood cultures, neutropenia, signs of systemic infection, and a history of vascular grafts or implanted prostheses.

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24 Principles of Radiation Oncology

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INTRODUCTION

Radiation oncology is the practice of using focused high-energy electromagnetic radiation to treat oncologic diseases. Radiation can be delivered in a variety of forms, each having different physical characteristics that offer unique advantages in individual patients. The total radiation dose and its fractionation vary, depending on the clinical goals of each patient's overall treatment plan. Radiation therapy can be given concurrently with chemotherapy, as adjuvant therapy, or primary therapy for a wide range of malignancies and can result in superior patient outcomes. At the MD Anderson Cancer Center, as a general rule, preoperative chemoradiation is preferred over postoperative chemoradiation because of the former's lower toxicity and superior tumor control.

BASIC RADIOBIOLOGY AND PRINCIPLES OF FRACTIONATION

Radiation kills tumor cells by irreversibly damaging their DNA; in general, the higher the total radiation dose is, the greater the likelihood that tumor cells will be killed. Tissues and organs have known dose and volume tolerances to late radiation injury that must be respected to avoid permanent late toxicity. The total radiation dose and the technique used to deliver it are typically chosen in an effort to limit a patient's risk of developing late complications from radiation treatment. Some organs such as the liver, lungs, and kidneys can tolerate large tissue-ablative doses to small tissue volumes without disruption of function. This is because destruction of a small part of the organ does not affect its overall function. Known volumes of these organs can safely receive lower doses of radiation without impairing their function. Other organs, such as the spinal

cord and gastrointestinal tract, cannot tolerate tissue-ablative doses delivered to one part of the organ without the overall function of the organ being affected. In these structures, the *maximum radiation dose* is the dose above which late injury is caused to any part of the organ. Four radiobiologic cellular processes—repair, repopulation, redistribution, and reoxygenation—dictate the optimization of fractionation.

Repair

All cells have the ability to repair some of the DNA damage caused by radiation. Normal cells can repair sublethal DNA damage much more effectively than tumor cells can; however, this superior cell-repair ability of normal cells is generally lost with increasing doses per fraction because the mounting double-strand DNA damage from higher doses overwhelms the cells' ability to repair it. The solution is to deliver radiation in smaller doses per daily fraction (1.8 to 2.0 Gy/day), which can kill tumor cells without permanently harming normal cells. In general, smaller doses of radiation per fraction enable a higher total radiation dose to be delivered. In some settings, however, larger doses per fraction can be safely delivered for a lower total radiation dose to the tumor. Fraction doses as high as 25 Gy that are delivered to small volumes may be clinically tolerable if no critical structures are near the target. For example, the use of stereotactic radiation therapy to deliver high doses per fraction to lung and liver tumors is tolerable because ablating the tissue surrounding such tumors does not affect organ function.

Repopulation

Repopulation refers to the ability of tumor cells to repopulate during a course of radiation treatment, which can happen if the time to deliver the full course of radiation is too long. Shortening the period between radiation doses may increase the probability of killing all tumor clonogenic cells. However, the amount to which these periods can be shortened in a course of standard fractionation radiotherapy is limited by acute toxicities to the tissues. Therefore, the benefits of complete tumor eradication must be weighed against the acute toxicities of radiation when doses are given closely together.

Redistribution

Redistribution refers to the distribution of tumor cells in different stages of the cell cycle. In each phase of the cell cycle, a cell has a different sensitivity to radiation. Redistribution is not routinely exploited in general radiation oncology practice.

Reoxygenation

Reoxygenation is the process in which hypoxic, radioresistant tumor cells become increasingly radiosensitive as they are exposed to oxygen with subsequent radiation fractions. Oxygen stabilizes radiation-produced free radicals, which leads to ionization, DNA strand breaks, and ultimately cell death in tumors. When a tumor reaches a diameter of 3 to 5 mm, it outgrows its blood supply and develops hypoxic areas that are radioresistant. When the tumor is irradiated, oxygenated (and thus radiosensitive) cells on the periphery of the tumor die, causing the tumor to shrink and allowing oxygen to diffuse to hypoxic areas, reducing treatment resistance.

Fractionation

Radiation oncologists fractionate total radiation doses to preserve normal cells and kill tumor cells. *Fractionation* is the process of dividing the total radiation dose into smaller, equal doses that are delivered over time. Fractionation exploits the inherent biologic differences between normal cells and tumor cells. It allows normal cells time to recover between fractions, unlike tumor cells, which are less efficient in cellular damage repair. It also allows tumor cells in a relatively radioresistant phase of the cell cycle during one treatment to enter into a more sensitive phase of the cell cycle for the subsequent fraction.

Typically, radiation dose fractions are delivered daily over the course of 2 to 7 weeks. Standard radiation dose fractions range from 1.8 to 2 Gy. *Hypofractionation* refers to the delivery of larger doses per fraction of radiation (>2 Gy) over a shorter overall time. Hypofractionated regimens are typically given in the palliative care setting. *Accelerated fractionation* refers to the delivery of standard fraction sizes given in a shorter overall time, often twice daily. *Hyperfractionation* refers to the delivery of a higher total radiation dose via smaller-than-standard doses per fraction. The goal of giving hyperfractionated treatment is to further exploit the difference in normal cells' and tumor cells' ability to repair sublethal DNA

damage. For example, delivering 1.2 Gy twice daily may enable a 10% higher total dose to be delivered because the normal tissue can better tolerate the smaller dose fractions. Radiation fractions can be given twice daily without damaging normal tissues because the time required for these tissues to repair sublethal DNA damage is believed to be between 4 and 6 hours.

BASIC RADIATION PHYSICS

Radiation can be delivered externally via low- or high-energy beams or internally via implanted radiation sources. The method of radiation delivery depends on the type and location of the tumor, as well as the patient's overall health. Radiation is most commonly delivered with high-energy electromagnetic radiation (x-rays or photons) that penetrates tissues to varying degrees, depending on the energy of the beams. Generally, beams with energies between 6 and 18 MV are used. The decision to use one type of beam versus another depends on the distance of the lesion from the skin's surface. In general, lesions closer to the surface of the skin are treated with lower-energy photons.

External Beam Radiation

External beam radiation can be delivered in the form of photons, electrons, or protons. Photon beams (x-rays or gamma rays) penetrate the body, irradiating both the tumor and the normal tissue. Electrons are subatomic negatively charged particles that only partially penetrate the body, depositing their energy at a depth that is dependent on the initial energy of the beam. Electron beams can be used to treat tumors within 6 cm of the surface of the skin.

Proton Therapy

Protons are charged particles that provide no exit dose beyond the target, resulting in sparing of normal tissue. Protons are likely to be more beneficial in pediatric patients by reducing the risk of long-term radiation toxicities. The clinical advantages of using protons over photons are being investigated in various disease sites. At MDACC, there are numerous ongoing clinical trials in multiple disease sites, including head and neck, breast, prostate, pediatric CNS, esophageal and thoracic, evaluating the

potential benefits of proton therapy versus intensity-modulated radiation therapy (IMRT). Early results have alluded to lower toxicity profiles with the use of protons in these disease sites.

Brachytherapy

Patients may also be treated with brachytherapy, the practice of directly delivering radiation by placing radioactive sources near the tumor or tumor bed. Brachytherapy offers advantages over external beam radiation because it can be used to deliver very high doses of radiation directly to the tumor while sparing surrounding normal tissues. Accurate placement of the source using an applicator positioned directly on the tumor or tumor bed allows for the most conformal of therapies. In general, the level of radiation diminishes with the square of the distance from the radioactive source. Factors that are considered when choosing a radioactive source for brachytherapy include the source's amount of radioactivity per gram (its "specific activity"), its half-life of radioactive decay, and the energy of the photons or electrons it emits. Common uses of brachytherapy with curative intent include temporary cesium placement for cervical cancer, temporary iridium-192 placement for a variety of tumors, permanent iodine-125 seed implantation for prostate cancer, and permanent gold-198 seed implantation for various malignancies.

Source activity, dose rate, and source-to-tumor exposure time are all considered when planning therapy and help dictate the modality used. High-dose rate (HDR) and pulse-dose rate (PDR) brachytherapy are commonly used for gynecologic malignancies including cervical, vaginal, and endometrial cancers. Low-dose rate brachytherapy is commonly used for prostate cancer. Indications for brachytherapy include locally contained, small-volume disease that can be accessed by an applicator device.

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT), a form of brachytherapy, is defined as radiation that is delivered to the tumor or tumor bed during surgery. There are many benefits to IORT including increased local control, ability to deliver higher doses of radiation, and increased delivery of radiation to the region of interest with minimal dose to surrounding tissue. IORT is usually used in conjunction with preoperative external-

beam radiation therapy. It is a helpful technique for gastrointestinal malignancies, such as recurrent or locally advanced colorectal cancers.

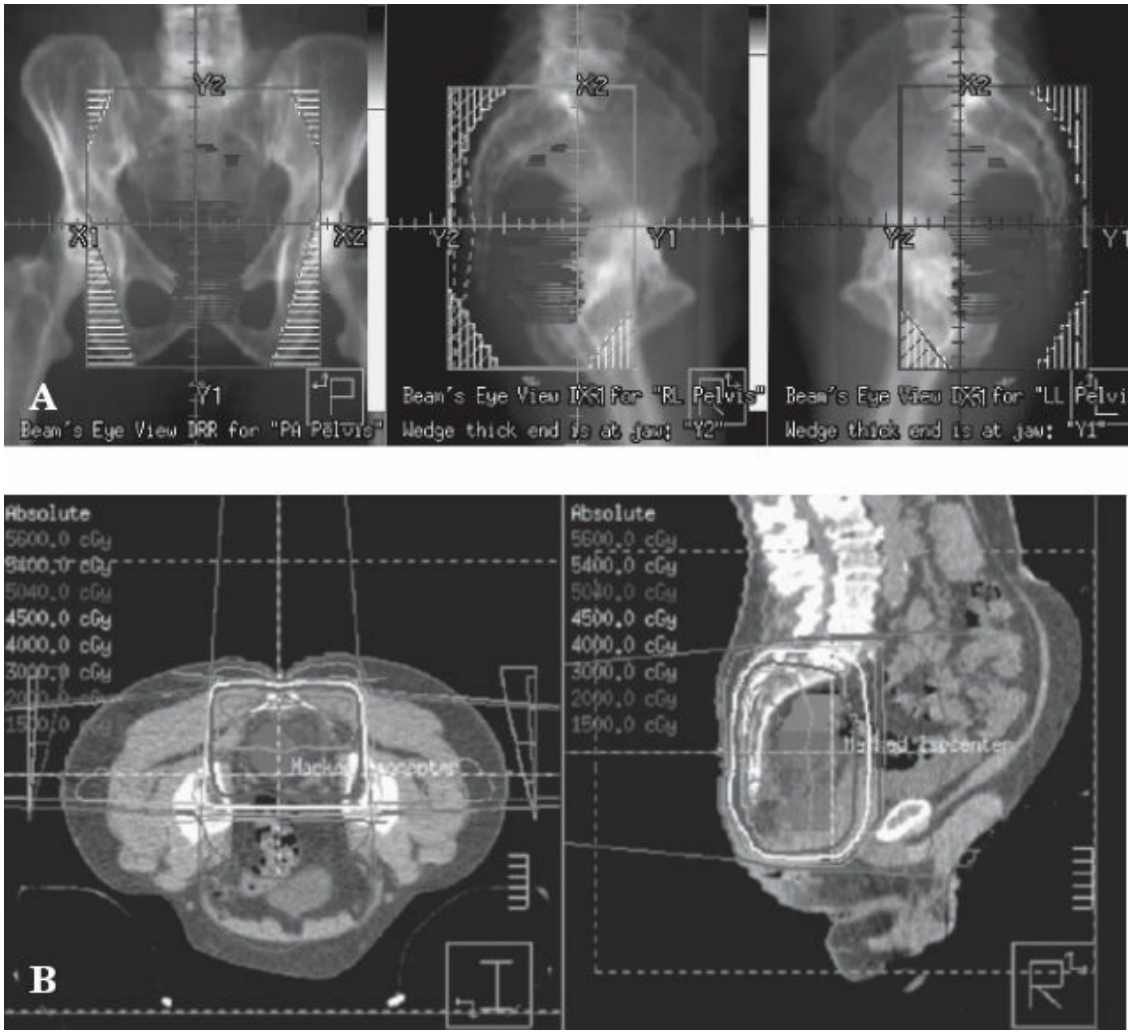

Figure 24.1 Three-dimensional plan for treatment fields (**A**) and dosimetry (**B**) for a patient receiving neoadjuvant chemoradiation. The lines surrounding the treatment volume in (**B**) represent the dose levels delivered to the planned volume and surrounding tissues.

IORT can be delivered as intraoperative electron radiation therapy or as HDR-IORT. Intraoperative electron radiation therapy uses electrons, and HDR-IORT uses HDR brachytherapy delivered through catheters. Both techniques deliver a high dose to the tumor region and minimize the dose to the surrounding normal tissue.

Radiation Dosimetry

In modern radiation oncology practice, radiographic imaging is used to

plan treatment that targets tumors while physically avoiding normal tissues to the greatest extent possible. *Radiation treatment planning* or *dosimetry* involves the creation of an optimized virtual treatment plan. Three-dimensional (3D) computed tomography (CT) images are used to design radiation fields and dose calculations, and blocking is used to block normal tissue structures (Fig. 24.1). A dose–volume histogram (Fig. 24.2) graphically represents the treated volumes of the tumor and the regional target that receives various doses (Fig. 24.1).

Conventional Radiotherapy

Conventional radiotherapy delivers radiation in rectangular-shaped fields with additional blocks and wedges. This form of radiation therapy is delivered by using beams that are conformed to the shape to the area of interest (e.g., tumor, nodal stations) in hopes of minimizing the radiation dose to surrounding healthy tissue. Conventional radiotherapy (3D-CRT) is commonly used to treat cervical cancer, rectal cancer, and breast cancer.

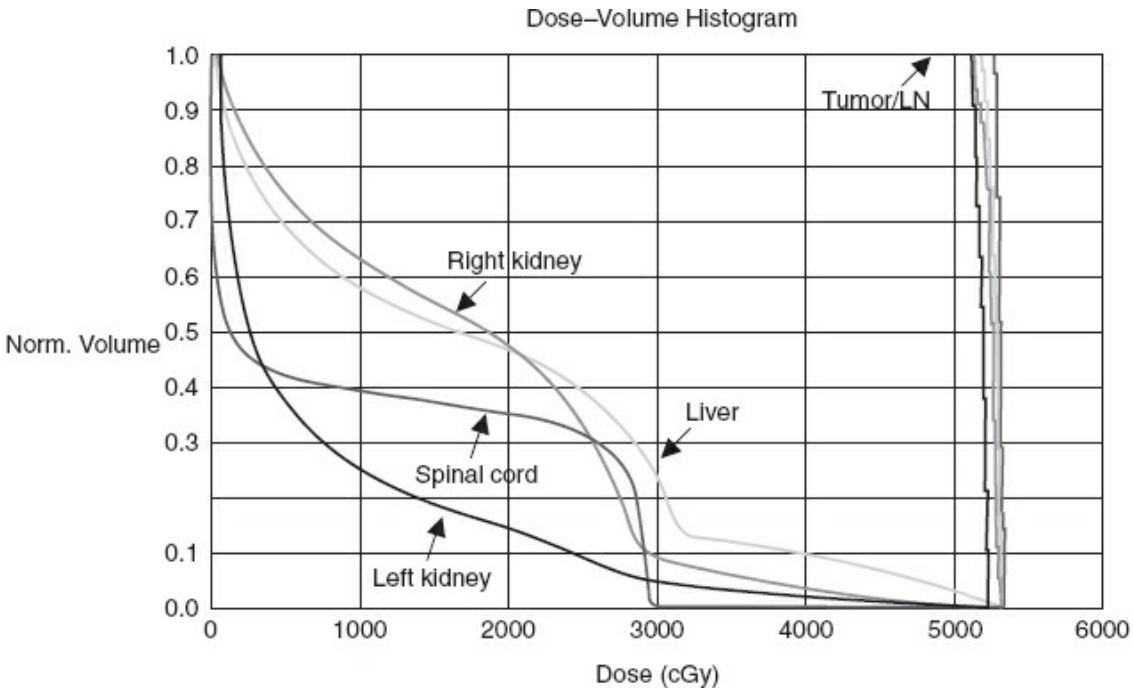

Figure 24.2 A dose–volume histogram graphically represents the treatment volumes and the various radiation doses received. Dose–volume histograms enable radiation oncologists to objectively assess the safety of a radiation treatment plan and the adequacy of organ coverage.

Intensity-Modulated Radiation Therapy

IMRT allows for the delivery of radiation consisting of variable intensities through a single beam. In addition, inverse planning allows for radiation to be delivered using multiple beam angles. This further helps reduce toxicity to surrounding tissues and maximizes dose delivery to the region of interest. IMRT is commonly used in head and neck, esophageal, pancreatic, and anal malignancies.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) uses radiation beams aimed at specific targets in the head and spine regions. A multidisciplinary approach is critical, with the involvement of neurosurgery, radiation oncology, and medical oncology, in order to accurately and safely treat these intracranial and intraspinal tumors. A Gamma Knife is a subtype of SRS that uses multiple cobalt-60 sources of radiation to deliver beams in a noncoplanar fashion, resulting in less dose to surrounding normal brain tissue.

Stereotactic Body Radiation Therapy

Applying the same principles of SRS, which targets the head and spine, stereotactic body radiation therapy (SBRT) was developed to provide more targeted radiation therapy to the rest of the body. SBRT is commonly used in thoracic and gastrointestinal malignancies and metastases. SBRT uses multiple conformal beams along with image guidance to allow for the delivery of higher ablative doses of radiation to the tumor in a limited number of fractions.

IMRT (Fig. 24.3) and SBRT deliver a radiation dose that conforms more precisely to the tumor than does a radiation dose delivered with conventional means. Both IMRT and SBRT involve inverse planning. The radiation oncologist contours the tumor target, any regional nodal targets, and the organs at risk for radiation damage on a CT scan. Then, the computer optimizes the dose distribution in the context of the normal tissue dose constraints that the radiation oncologist has specified. In IMRT, the radiation beam is divided into hundreds of tiny beams that turn on and off, resulting in highly customized dose distributions. This form of radiation planning and delivery is particularly useful for fractionated radiation therapy in which high doses of radiation can be delivered while critical structures are protected.

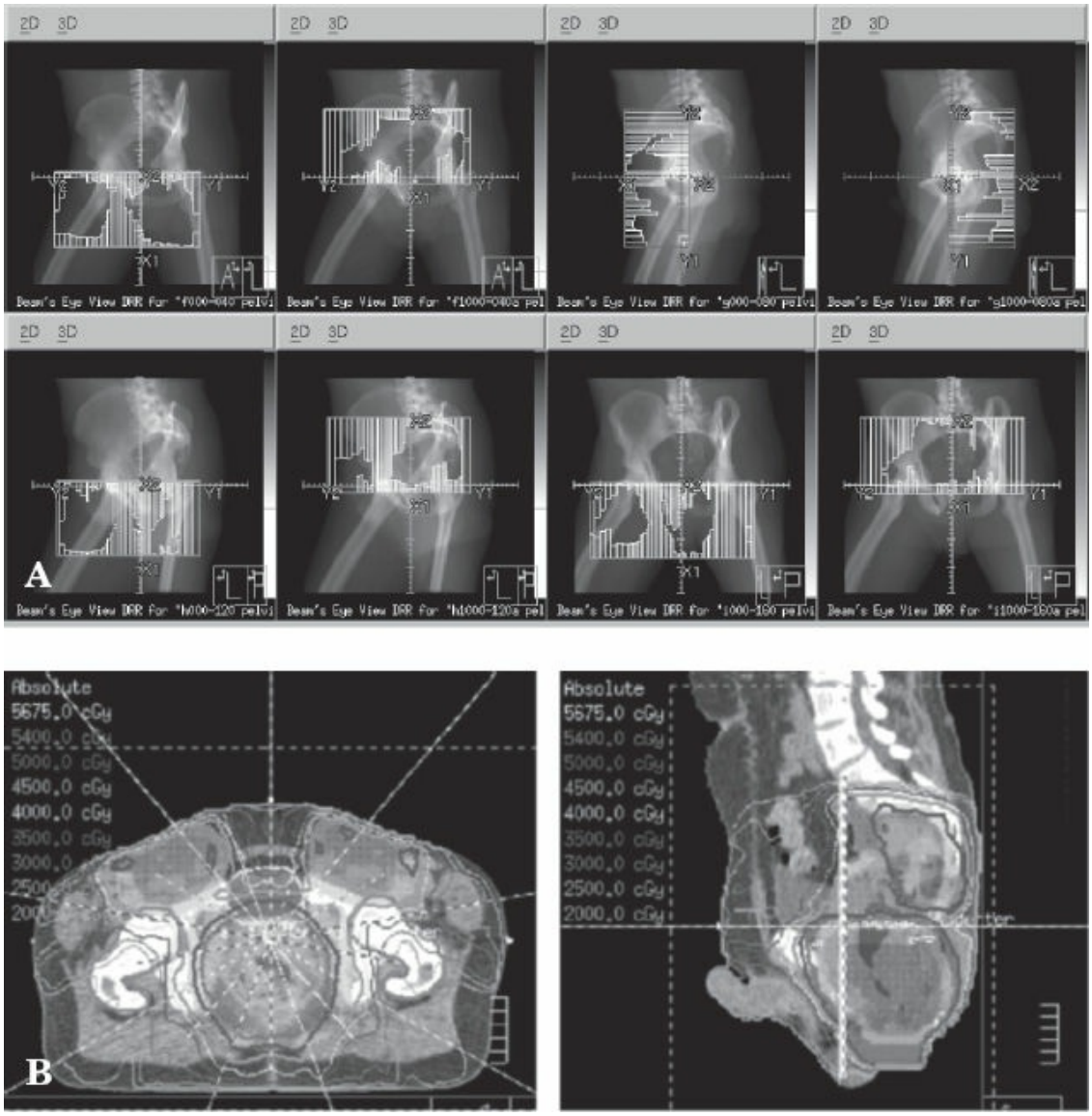

Figure 24.3 Intensity-modulated radiation therapy (IMRT) allows for optimal sparing of normal tissues and for the possibility of improved local tumor control with use of higher radiation doses. IMRT for anal cancer is one of the best uses for this therapy. IMRT spares the genitalia, thereby reducing toxicity and improving sexual function long term. Treatment fields (**A**) and dosimetry (**B**) for a typical IMRT plan are shown.

Image-Guided Radiation Therapy

In image-guided radiation therapy, imaging studies are used to verify that the radiation delivered during treatment is in accordance with the radiation delivery that was planned with use of the patient's initial CT scans. It enables a more accurate setup in the delivery of treatment by ensuring that the tumor is not missed. Other reasons for using image-guided radiation

therapy are to prevent day-to-day setup uncertainty, to accurately position the patient over the course of treatment, to adjust for organ motion during treatment such as that due to gastric emptying or filling, and to account for tumor shrinkage out of the planned field of radiation, which may occur with radiosensitive tumors such as lymphoma and anal cancer. Daily x-ray and/or cone-beam CT studies (a limited CT scan obtained on the treatment machine immediately before treatment) are commonly used to guide radiation therapy.

Chemoradiation

Postoperative adjuvant chemoradiation was first used in the 1980s to treat rectal cancer patients. It has served as a model for other gastrointestinal sites. In virtually every tumor site where combined modality approaches are standard (e.g., head and neck cancer, gastrointestinal cancers), chemoradiation contributes to locoregional disease control of 90% or greater by eradicating microscopic residual disease in the tumor bed after complete tumor resection or by reducing disease recurrence in regional lymph nodes. For most tumor sites, the patients who benefit the most are those with T3 or T4 tumors, lymph node involvement, or microscopically close or positive surgical margins.

Preoperative chemoradiation has been shown to be more effective and less toxic than postoperative chemoradiation for many patients, likely because with the former, the chemotherapy is delivered with an intact blood supply, and hypoxia-related chemoradiation resistance is avoided. In the specific setting of gastrointestinal irradiation, preoperative chemoradiation results in less acute toxicity than postoperative chemoradiation due to the greater ability of the preoperative procedure to avoid gastrointestinal mucosal irradiation. After gastrointestinal surgery, the small bowel is fixed in the tumor bed and/or the gastrointestinal tract anastomosis will have to be irradiated, which increases the risk of mucosal or anastomotic injury. In contrast, with preoperative chemoradiation, the irradiated gastrointestinal tract with the targeted tumor is removed during surgery, and healthy bowel is used in the reconstruction, considerably lowering the possibility of late radiation injury to these structures. The assertion that preoperative chemoradiation offered advantages over postoperative chemoradiation was controversial until the question was successfully tested in a randomized phase III trial in rectal cancer patients (Sauer et al.). Patients who received preoperative chemoradiation had

improved sphincter preservation, better local tumor control, and lower rates of acute and late toxicities (such as anastomotic strictures and chronic diarrhea) than did patients who received postoperative chemoradiation.

Preoperative chemoradiation also offers unique advantages in patients with poor performance status, high operative risk, or high risk of distant metastasis. Most compelling is that preoperative chemoradiation offers the ability to treat virtually all patients who present with localized, resectable cancer with therapy that immediately addresses the limitations of curability—namely, micrometastatic disease. In contrast, delayed recovery from surgery can prevent the timely initiation of postoperative chemoradiation (optimally within 6 to 8 weeks after surgery), thus limiting its efficacy and enabling residual microscopic clonogenic cells to repopulate to gross residual disease. An additional benefit of preoperative chemoradiation is that it facilitates patient selection for complex surgeries that have a significant risk of morbidity or mortality by identifying patients who would not do well with surgery.

RADIATION SIDE EFFECTS

In normal tissues, radiation reactions are classified as either acute reactions or late reactions. Acute radiation reactions are due to the temporary depletion of rapidly dividing cells. Common acute radiation reactions include skin desquamation, nausea, diarrhea, and reduced blood cell counts. After an acute radiation reaction, progenitor cells repopulate the tissue, and the effects of the acute reaction resolve. In contrast, late radiation reactions, which can include severe fibrosis, transverse myelitis of the spinal cord, blindness, and pulmonary fibrosis, are caused by microvasculature damage or the depletion of terminally differentiated cells. These late reactions are much less likely to resolve.

RADIATION SAFETY

Time, distance, and shielding should be considered in order to protect health care personnel and patients from radioactive sources. Specifically, the following should be noted.

1. Health care personnel should minimize the amount of time they spend in close proximity to radiation sources. The highest levels of radiation exposure occur during procedures that require the use of fluoroscopy.
2. Since the level of radioactivity falls off with the square of the distance

to the radiation source, maximizing one's distance from the source diminishes one's exposure to radiation. Radioactive sources should never be touched directly.

3. Shielding is an important aspect of radiation protection. All linear accelerators, CT scanners, and x-ray tubes are shielded in lead- and/or concrete-encased rooms; thus, exposure to radiation for most hospital personnel is minimal. However, shielding is much more of a challenge for personnel who work more directly with radiation sources. In general, lead aprons are effective protection against low-energy radiation sources such as traditional diagnostic and fluoroscopic x-rays.

MULTIDISCIPLINARY APPROACH

Multidisciplinary clinics (MDCs) are becoming increasingly prevalent in the management of oncologic disease. MDCs establish a common forum for specialists in radiation oncology, medical oncology, surgery, radiology, pathology, palliative/supportive care, nutrition, and social work to discuss patient cases and formulate a coherent, organized management plan. The practice model of MDCs has been shown to increase the accuracy of initial staging and improve survival for patients with breast, ovarian, and pancreatic cancers. Moreover, the multidisciplinary approach reduces time to treatment and patient anxiety, increases patient exposure to support services and resources, improves overall patient satisfaction, and increases enrollment into clinical trials.

SUMMARY

Chemoradiation has been shown to improve locoregional control and survival in a variety of cancer patients. The use of preoperative chemoradiation is based on biologic factors such as tumor oxygenation and on clinical factors such as the avoidance of normal tissue irradiation and selection of the best candidates for curative surgery. The choice of radiation modality and treatment planning technique is based on the goal of achieving the optimal dose distribution. Typically, complex treatment plans are needed when the tumor is located near critical structures such as the spinal cord and bowel. Newer technologies such as proton therapy, IMRT, SRS, SBRT, and image-guided radiation therapy have enhanced our ability to give higher radiation doses to targets while reducing normal

tissue exposure.

Recommended Readings

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25 Reconstructive Surgery in Cancer Patients

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INTRODUCTION

In cancer patients who have undergone extirpative surgery, the goal of reconstructive surgery is to restore form and function. This goal is best accomplished by replacing the resected tissue—bone, skin, fat, etc.—with similar tissue. Reconstructive options vary from simple to complex based on the needs of the wound and patient. Simple procedures include primary closure, local tissue rearrangement, and skin grafting. More complex procedures include the use of pedicled flaps or microvascular free flaps. The ability to perform complete oncologic resections has increased with our ability to perform reconstructive surgery more safely and reliably with decreased morbidity.

GENERAL PRINCIPLES OF RECONSTRUCTIVE SURGERY

To select the appropriate reconstructive technique, it is critical to evaluate physiologic status of the patient. A patient with multiple comorbidities or poor nutrition may not be able to tolerate a lengthy procedure and therefore should instead be treated with a more conservative type of reconstruction. In contrast, a patient with adequate physiologic reserves may be best served by a more technically complicated procedure, such as microsurgical reconstruction, when it provides the optimal restoration of both form and function.

In addition to wound closure and maintenance of function, an important goal of reconstructive surgery is aesthetic restoration. While most people may immediately associate aesthetics with cosmetic surgery, aesthetics in the cancer patient focuses on the restoration of one's prior appearance and the ability to be out in public without the stigmata of cancer resection.

Many patients that present to the reconstructive surgeon have significant body image concerns and anxiety about their ability to interact with others, especially their loved ones, in the future. The goal of the reconstructive surgeon is to not only heal wounds, but allow patients to return to their lives feeling whole. It is not acceptable to close a wound that radically deforms the patient, if alternatives exist.

The timing of reconstruction is most often dictated by the status of the tumor and oncologic treatment. Reconstruction can be performed in an immediate or delayed fashion. Immediate reconstruction is considered when a patient needs restoration of a vital structure, such as the pharynx or abdominal wall, or when their physiologic reserve allows extended time under anesthesia. When immediate reconstruction is performed, tissue planes are readily accessible and the wound bed has little or no fibrotic tissue. In contrast, when the reconstruction is delayed, scar tissue, fibrosis, and wound contracture can inhibit optimal aesthetic and functional outcomes. However, delayed reconstruction may be necessary when margins are not clear, as in permanent section evaluation for melanoma, or when the patient requires significant postoperative radiation that will damage the reconstruction, such as in breast reconstruction.

RECONSTRUCTIVE TECHNIQUES

The core principle of the reconstructive algorithm is to progress from simple to more complex reconstructions on the basis of the specific wound requirements. This is referred to as the “reconstructive ladder.” The primary goal is to close a wound with tissue that will be tension free and obliterate any dead space. Furthermore, it will be durable and functional if possible. In general, primary closure is the simplest and lowest rung of the ladder. Skin grafts may be considered next. When insufficient, local flaps may close more complex wounds. Finally, microsurgical techniques may be required to transfer free autologous tissue from one area of the body to another when local options are not available. Additionally, when reconstruction is not immediately necessary, local tissue may also be “expanded” to cover a defect.

Skin grafts contain epidermis and variable amounts of dermis. A partial-thickness skin graft includes superficial dermis, whereas a full-thickness graft includes the entire dermis. Skin grafts require a vascularized bed for ingrowth, such as granulated tissue, fascia, muscle, or periosteum. Because full-thickness skin grafts contract less than split-thickness skin grafts, full-

thickness grafts are preferable in regions where wound bed contraction is not desirable. For example, they are frequently used on the face, where wound bed contraction near the eyelids, nose, or mouth would compromise aesthetic and/or functional outcome. Aesthetic outcomes are inferior to those of local or free-tissue flap options in many instances due to minimal tissue thickness and color match.

Local and regional flaps enable surgeons to reconstruct wounds with similar tissue from a nearby location. The tissue that is moved is called a "flap." "Random" local flaps are usually comprised of adjacent skin and subcutaneous tissue that are based on a subdermal plexus vascular supply. By definition, random flaps do not have a distinct, named blood vessel as their source of nourishment. As such, they are generally limited in size with 3:1 length to width ratio. In contrast, "pedicled" flaps are based on named blood vessels, including an arterial and venous pedicle. These flaps can be moved as far as their vascular pedicle will allow, and may not necessarily be from an adjacent location, hence, they are considered regional flaps. A pedicled flap may be very small or large depending on the area perfused by the pedicle blood vessels. For example, a nasolabial flap is a small flap based on the angular artery, a branch of the facial artery, and is approximately 4 × 1.5 cm, both because it is a small blood vessel with a limited vascular territory and because it is difficult to close the donor site primarily if wider than about 1.5 cm. In contrast, a latissimus dorsi muscle pedicled flap can be as large as 30 × 40 cm. Pedicled flaps can be cutaneous, fasciocutaneous (deep muscle fascia with overlying skin), muscular, myocutaneous (muscle with skin), osseous, or osteocutaneous (bone with overlying skin), which enables reconstructive surgeons to repair defects with tissue that is similar to the resected tissue.

Microvascular free flaps are tissues and their pedicle blood supply from a distant region of the body that are transferred to a defect. Vascular anastomoses between the flap's donor (pedicle) vessels and recipient vessels within or near the defect are performed under magnification provided by a microscope or high-powered surgical loupes. They are called "free flaps" because they become free of their native vascular origin. The decision to use a particular flap is based on the requirements for replacing missing skin, adipose tissue, fascia, muscle, and/or bone. The primary advantage of microvascular free tissue transfer is that tissue of a quality similar to that of the resected tissue can be moved from a remote part of the body, enabling optimal aesthetic and functional outcomes.

Drawbacks of free tissue transfer are related to donor-site morbidity, the potential for long operative times, and possible complications with the vascular anastomoses. However, when performed with appropriate technique and efficiency, free flaps are highly reliable and often the best choice for reconstruction for both form and function.

Tissue expansion is a process in which an inflatable prosthetic implant with a silicone shell is used to expand local and regional tissues. In breast reconstruction, they are used to stretch or "expand" the remaining mastectomy skin for future implant placement. In other defects, the skin is expanded so that it can eventually be advanced into the wound for coverage in a delayed fashion. The inflatable implant is inserted at the time of tumor extirpation or during a second procedure. At subsequent office visits, saline is injected through an integrated or remote port to gradually expand the implant. Once the tissue has been sufficiently expanded, the expander is removed and the tissue is used for wound coverage or as an implant pocket, in the case of breast reconstruction. Risks of tissue expansion include implant exposure, infection, and pain related to serial expansions.

HEAD AND NECK RECONSTRUCTION

The goals of reconstruction in the head and neck often include preservation of speech, swallowing, and masticatory function, maintaining an airway while preventing aspiration and velopharyngeal insufficiency, supporting the orbit, and maintaining the appearance of the face. Coverage of the facial bones, dura, and brain, as well as the neurovascular structures of the neck may also be indications for reconstructive surgery. Each region of the head and neck has specific reconstructive needs and challenges are usually best reconstructed as separate subunits. With a few notable exceptions described below, microvascular free flaps are usually associated with superior outcomes and the preferred reconstructive method for most patients undergoing all but the most limited resections.

Scalp and Calvarium

The scalp, including the forehead, is a well-vascularized region composed of five layers that can be remembered using the mnemonic *SCALP*: *S*kin, sub*C*utaneous tissue, galea *A*poneurosis (a dense fibrous connective tissue layer interspersed between the frontalis, occipitalis, and temporalis

muscles that fuses with the temporoparietal fascia at the temporal crest), *L*oose areolar tissue, and *P*ericranium (the periosteum covering the calvarial bones).

The reconstructive method of choice depends on surface area and depth of the wound. If the pericranium remains intact, one option is to allow the wound to heal by secondary intention or resurface the wound with a split- or full-thickness skin graft. Skin grafting of course results in an area of alopecia that may be noticeable in patients who are not bald.

Because the scalp is poorly distensible, only very small full-thickness wounds can be closed primarily, even with wide undermining in the loose areolar plane deep to the galea aponeurotica. Scoring the galea at right angles to the direction of advancement decreases wound tension and may allow primary closure of wounds up to 3 cm wide. Care needs to be taken not to injure the blood vessels that lie above the galea, which could compromise the viability of the scalp.

Defects greater than 3 cm but less than 6 cm can generally be reconstructed with one or more rotation flaps. Larger defects can be closed with rotation flaps and skin grafting of the flap donor site, provided there is intact pericranium. Such “scalping” flaps may result in a cosmetically unfavorable “bald” spot if the skin-grafted donor site is noticeable in a patient with an otherwise full head of hair. The base of each rotation flap should contain an intact named blood vessel (i.e., supraorbital, supratrochlear, superficial temporal, post auricular, or occipital) to serve as an axial blood supply. In some cases, wounds approaching 50% of the scalp surface area can be closed with a scalping flap or skin grafted if the periosteum is intact, then tissue expansion of the hair-bearing scalp can be performed so that the skin-grafted area can be removed. The risks of tissue expansion include exposure of the expansion device, infection, and decreased hair density inherent to the expansion process. Irradiation is a relative contraindication to tissue expansion due to the high rate of exposure and poor expansion of radiated tissue.

Defects larger than about 6 cm, or even smaller defects in irradiated scalps, usually require microvascular free flap reconstruction. The scalp can usually be reconstructed with thin cutaneous or fasciocutaneous free flaps, such as the anterolateral thigh (ALT) free flap in most patients, or a muscle flap, such as the latissimus dorsi muscle free flap, covered with a skin graft. For the largest defects, the latissimus dorsi muscle free flap is usually considered the flap of choice due to its large surface area, often

sufficient to resurface the entire scalp. The superficial temporal blood vessels are the preferred recipient blood vessels for free flap reconstruction, but may not be available due to ligation during prior surgeries. In such cases, vein grafting may be needed to reach recipient blood vessels in the neck.

Occasionally, skin cancers of the scalp can invade the underlying bone, necessitating removal of the outer-table or full-thickness calvarium, depending on the depth of tumor involvement. The repair of such defects requires autologous bone grafts such as split-calvarial grafts or prosthetic materials such as titanium mesh or methyl methacrylate in addition to free flaps. Well-vascularized coverage over grafts and implants is mandatory. As long there is no gross contamination, simultaneous scalp and calvarial reconstruction is usually safe and reliable. In the setting of infected bone or prosthetic, scalp reconstruction followed by delayed cranioplasty is usually recommended.

Face

Facial reconstruction can be divided into specific units, each with its own anatomy and function: cheek, eyelids, nose, lips, and neck. Each region must be considered independently and collectively when defects cross facial zone boundaries.

Cheek

Small defects of the facial skin can often be closed primarily after an elliptical incision. Such an incision should be made in the direction of the facial skin-tension lines. If the wound cannot be closed primarily without significant distortion of the face, the next option would be a local tissue flap based on a random blood supply. Moderate medial cheek defects of up to about 5 cm can be closed with cervicofacial fasciocutaneous rotation flaps and even larger defects can be closed with cervicothoracic rotation flaps. The greater the amount of rotation needed, the greater the risk for ectropion of the lower eyelid as a complication. Full-thickness skin grafts can be used instead of local flaps or in addition to local flaps as long as bone or neurovascular structures are not exposed, but may be prone to contraction. The best skin graft donor site for facial reconstruction is the region above the clavicle or the preauricular or postauricular skin, because of the good color and texture match to the rest of the facial skin. Skin

grafts are usually avoided when postoperative radiation therapy is planned due to concerns for graft loss or contracture. When a wound cannot be covered with local tissue, reconstruction with cutaneous or fasciocutaneous free flaps, such as the ALT or parascapular free flaps, may be necessary.

Nose

The nose consists of nine aesthetic subunits: the dorsum, two sidewalls, the tip, the columella, two soft triangles, and two alae. The adage to replace “like with like” is critical in this anatomical region, and, therefore, local and regional flaps are the mainstay of nasal reconstruction. A possible exception is use of full-thickness skin grafts on the dorsum of the nose, where the native skin tends to be thin and contracture is unlikely to distort the shape of the nose. Nose defects involving <50% of an aesthetic subunit can be reconstructed with a local flap and the remaining subunit can be retained. However, the entire subunit should be reconstructed if the defect involves ≥50% of a subunit. Local flaps such as bilobed flaps can be used to reconstruct defects of the nasal sidewall and dorsum. The paramedian forehead flap, based on the supratrochlear artery, is the workhorse flap for most sizable defects, larger than about 1.5 cm in diameter up to the entire exterior nasal skin, because of its excellent color and texture match to nasal skin. Usually a secondary choice due to its thickness, the nasolabial flap, which is based on the angular artery, can also be used to reconstruct defects in the lower nasal elements. Full-thickness defects of the nose comprise the external skin, cartilage, and nasal lining, and all three layers must be considered in repair. The nasal lining often can be reconstructed with local flaps obtained from the nasal mucosa. Cartilaginous structures can be reconstructed using cartilage grafts from the rib or ear. The paramedian forehead flap is preferred for external skin coverage in full-thickness defects.

Lip

The vermilion–cutaneous junction, the border between the red of the lip and surrounding skin, is a distinct anatomical line that must be meticulously reconstructed. Asymmetries at the vermillion–cutaneous junction of greater than 1 mm will lead to visible irregularities in a reconstructed lip.

Defects less than one-third the width of the lower or upper lip are generally repaired with wedge resection and multilayered primary closure. For larger defects, a local flap, called a lip switch flap, must be considered. Lip switch flaps, also known as Abbé–Estlander flaps, are pedicled flaps transferred from the opposite lip that are based on the labial branch of the facial artery. Lip switch flaps are used to repair defects that are between one- and two-thirds the width of the lip.

Defects larger than one-half to two-thirds the width of the lip require bilateral rotation or advancement flaps, which recruit larger segments of tissue from adjacent cheek tissue. One such flap is the Karapandzic advancement flap, a neurovascular flap that preserves the elements of the facial nerve branches to the orbicularis oris. However, the use of advancement flaps can reduce the oral aperture, resulting in microstomia. Total lip defects are usually reconstructed with a free radial forearm flap suspended by a palmaris longus tendon graft that is secured from zygoma to zygoma to support the reconstructed lip and maintain lip height.

Ear

The outer ear is composed of skin closely adherent to an underlying cartilaginous framework. The surface anatomy of the ear consists of the helix, antihelix, concha, tragus, and lobule.

Small defects in the skin of the helical rim can be repaired with excision of a triangular wedge and direct approximation. If the defect is small but direct approximation cannot be performed, the remaining helix can be reconstructed with local chondrocutaneous flaps; in this instance, the remaining helical rim is dissected off the scapha and advanced. Large defects of the helical rim can be covered with a postauricular skin flap over a cartilage graft from the concha of the same or the contralateral ear to maintain shape. This is a staged procedure in which division of the base of the flap and completion of the flap inset are performed about 3 weeks after the initial transposition of the flap. A skin graft is usually applied to the denuded mastoid or temporal region at the flap donor site.

Large auricular defects with missing cartilaginous components can be reconstructed using cartilage grafts from the ribs. These grafts can be sculpted to conform to the missing helical rim and covered with a pedicled temporoparietal fascia flap based on the superficial temporal artery. Alloplastic frameworks such as those composed of high-density polyethylene can also be used to repair cartilaginous defects in the ear,

obviating the need for donor cartilage. Alloplastic implants should be covered with vascularized tissue such as a temporoparietal fascia flap. Alternately, substantial auriculectomy defects may be addressed with a maxillofacial prosthesis attached with adhesives of osseointegrated titanium implants embedded in the adjacent temporal bone.

Oral Cavity

The oral cavity includes the anterior tongue, floor of the mouth, alveolar ridges, retromolar trigone, hard palate, and buccal mucosa. Oral tumor resection results in a functional and aesthetic defect in the face and mouth. Defects involving any of these structures can compromise speech, chewing, swallowing, and breathing.

The thin, pliable fasciocutaneous forearm free flaps, based on either the radial or ulnar artery, are excellent options for reconstructing mucosal defects of the floor of the mouth and buccal area without creating bulk that interferes with function and does not restrict tongue movement or mouth opening, respectively. The lateral arm flap, which is supplied by the posterior radial collateral vessels, and the ALT flap may also be appropriate choices provided the patient has minimal subcutaneous fat in these areas. For full-thickness buccal mucosa–cheek defects, the radial or ulnar forearm free flaps or other fasciocutaneous flaps of appropriate thickness can be folded in on themselves to provide an internal and external lining.

Very small tongue defects can sometimes be skin grafted or allowed to heal secondarily. Free flaps should be considered for any defect in which contracture may limit tongue movement, which could impair speech, deglutition, or oral hygiene by inhibiting the sweeping function of the tongue used to clear food debris from the oral cavity. Partial glossectomy up to hemiglossectomy defects are also best reconstructed with a thin, pliable free flap, such as the radial or ulnar forearm fasciocutaneous free flaps (Fig. 25.1). Total and near-total glossectomies require bulky flaps to help prevent aspiration by directing food, liquids, and saliva away from the larynx and down the lateral pharynx into the esophagus. In most patients, the rectus abdominis myocutaneous free flap or the ALT free flap including a portion of the vastus lateralis muscle can provide adequate bulk for reconstructing total and near-total tongue defects. Prior to the advent of free flap reconstruction, many total glossectomy patients required laryngectomy to avoid chronic aspiration. In recent years, the

majority of such patients can avoid laryngectomy and up to half are able to sustain themselves partially or completely without feeding tube supplementation.

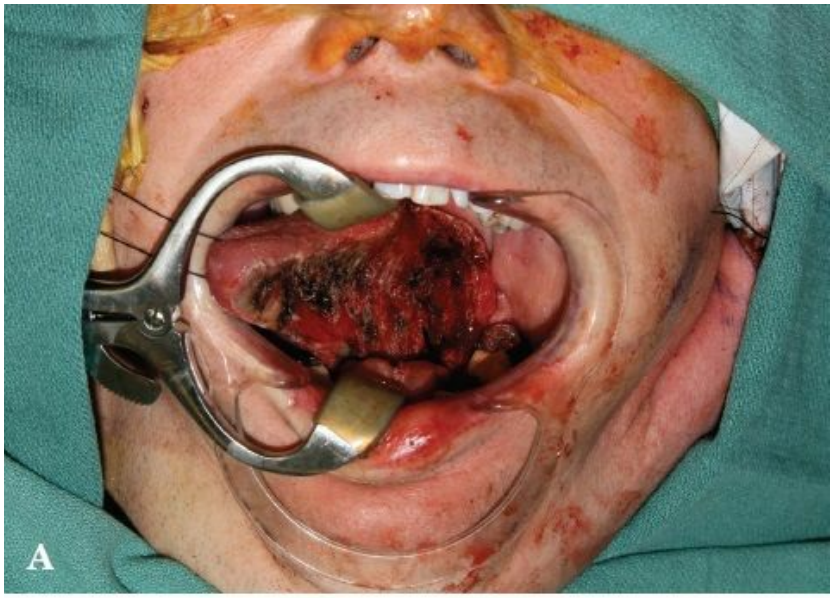
Mandible

The mandible plays a key role in mastication and giving shape to the lower third of the face, as well as deglutition, articulation, and stabilizing the airway based on its support and interaction with the tongue. Functional losses and aesthetic deformity depend on the size and location of the mandibular defect. Defects in the posterior body or ramus of the mandible are generally better tolerated than defects in the anterior mandible, which are associated with significant deformity and loss of function. Malocclusion may develop as a result of a shift in the position of the mandible following mandibulectomy. Mandibular reconstruction following ablative surgery optimally preserves mastication, speech, swallowing, and airway integrity. It restores lower facial aesthetics and enables subsequent dental reconstruction.

In mandibulectomy defect repair, the functional and aesthetic results obtained with microvascular tissue transfer are superior to those obtained with nonvascularized bone grafts or pedicled tissue transfers. Smaller segmental mandibulectomy defects, less than 5 cm, may be reconstructed with nonvascularized grafts and metal plates when adjuvant radiation is not planned, but such defects are rare following cancer resections. In most patients, mandibulectomy defects involve a large segment of the bony mandible, the internal oral lining, and, sometimes, the external skin. Free flap reconstruction provides sufficient bony and soft tissue coverage with a reliable vascular supply. Vascularized bone free flaps have high bone union rates because the flaps heal by primary bone healing, similar to how fractures heal. In contrast, nonvascularized bone grafts heal by osteoconduction.

The mainstay of mandibular reconstruction is the fibula osteocutaneous free flap. This flap provides up to 20 cm of bone. Because of its rich periosteal blood supply, osteotomies can be made to contour the bone such that it takes on the shape of the resected mandible without devascularization. In addition, a skin paddle can be harvested to provide soft tissue coverage. Functionally, harvest of the central fibula is well tolerated as long as 5 cm of proximal and distal fibula are preserved in situ for tibial stability. The length and caliber of the pedicle vessels are

sufficiently large to be anastomosed to vessels in the neck.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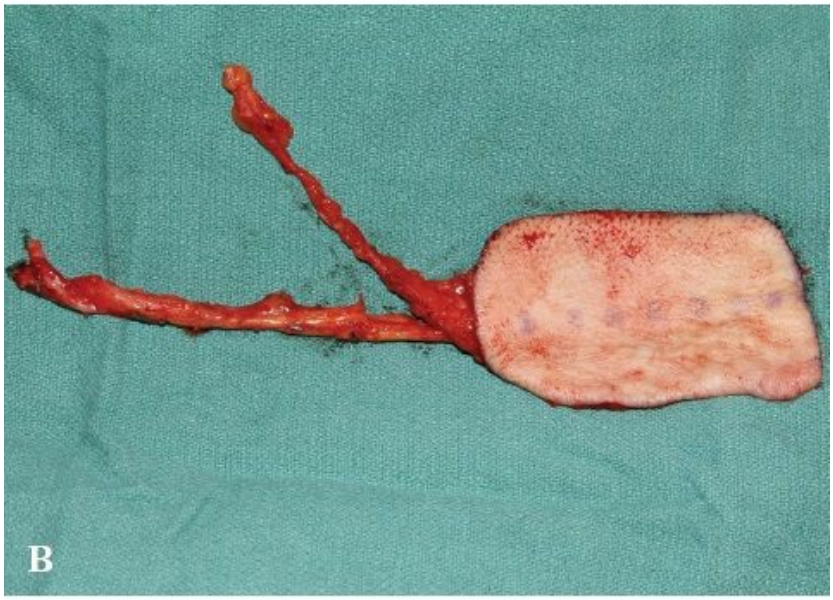
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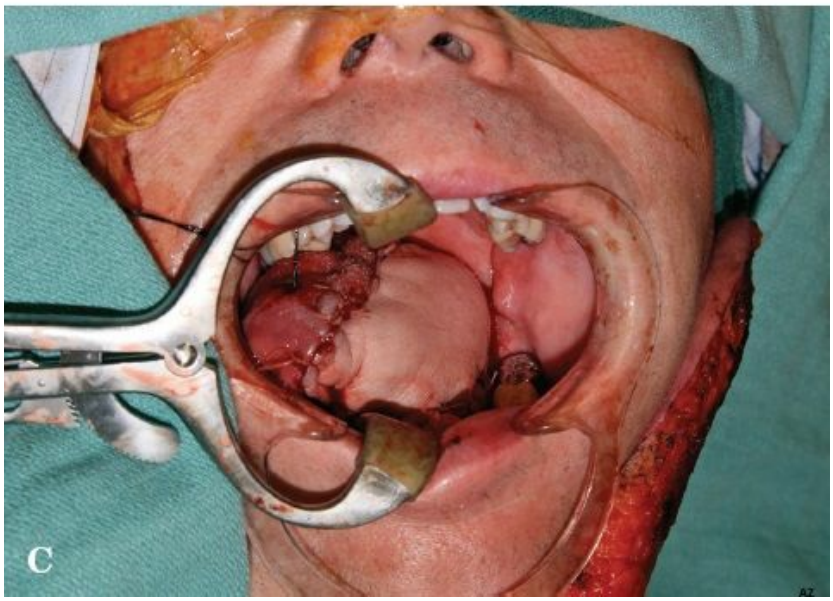
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Figure 25.1 A left hemiglossectomy defect (**A**) is reconstructed with a radial forearm free flap (**B**), which is a thin, pliable fasciocutaneous flap that is well suited to resurfacing the tongue without restricting its movement. **C:** Completed reconstruction.

The fibula flap is based on the peroneal artery and vein; therefore, its use requires that either the anterior or the posterior tibial vessels adequately perfuse the distal lower limb. An angiogram may be required to confirm this before harvest. Secondary flap sources for mandible reconstruction include the iliac, scapular, and radial bone free flaps.

Pharynx

The goal of pharyngoesophageal reconstruction is to restore swallowing and speech. Reconstruction of the pharynx and proximal esophagus is challenging. Most patients who require reconstruction also receive radiation therapy, which complicates reconstructive efforts.

Traditional methods of pharyngeal and esophageal reconstruction, including the use of tubed deltopectoral pedicled flaps, have given way to immediate reconstruction with jejunal segment, radial forearm, and ALT free flaps. Pharyngeal and esophageal reconstruction with the ALT free flap has been shown to result in a better voice restoration with a tracheoesophageal prosthesis (TEP) than reconstruction with the jejunal free flap, which results in a “wet” voice. Additionally swallowing is often interrupted by disordered peristalsis within the flap. Furthermore, harvest of a jejunal flap requires laparotomy and bowel anastomosis, with potential for greater morbidity in the setting of a complication. ALT free flaps and jejunal free flaps have similar rates of stricture formation and fistula formation. Both options are superior to nonmicrovascular alternatives.

BREAST RECONSTRUCTION

The treatment for breast cancer involves multiple modalities, including surgery (resective and reconstructive), systemic therapy (chemotherapy and/or hormonal therapy), and radiation therapy. From a reconstructive standpoint, one must consider the amount of breast parenchyma removed (mastectomy vs. partial mastectomy), the amount of skin remaining after surgical resection (skin-sparing vs. traditional mastectomy), whether

radiation may be required or has already been given, and the use and timing of systemic therapy.

Each type of breast reconstruction has its advantages and disadvantages. Some women desire no reconstruction at all. There is no one approach to breast reconstruction that is appropriate in all patients. Some aspects to consider in helping a patient choose the right reconstructive option include: (a) the patient's desires and expectations, (b) the treatment that they have undergone and still have to undergo, (c) their willingness to undergo surgery and (d) their overall prognosis with the disease. Although there are certain instances in which a single-stage reconstruction may be possible, in general, breast reconstruction is a process that entails multiple surgical procedures over the course of 4 to 12 months. These procedures include the initial breast reconstruction, any subsequent operations for achieving breast symmetry, and nipple reconstruction.

When counseling patients on reconstructive options it is important to remember that the primary focus of treatment is the cancer. Reconstruction is important, but it is a secondary goal. Women can often feel overwhelmed by all of the treatment options, not only in treating their cancer but also in the reconstruction. It is important to remember that every patient has different expectations for her body following treatment for breast cancer. Counseling patients on all options for reconstruction and then allowing patients to make their own decisions, leads to highest long-term satisfaction rates post treatment for breast cancer. It is additionally important to give patients a realistic idea of what to expect after reconstruction.

Timing Considerations for Breast Reconstruction

An important aspect to discuss with patients is the timing of breast reconstruction. This is based not only on the patient's wishes but also on the characteristics of the disease. Immediate reconstruction takes place at the time of the breast cancer surgery. Delayed reconstruction takes place later, after the treatment for the cancer is complete (Fig. 25.2). Immediate reconstruction results in the best aesthetic outcomes if postmastectomy radiation therapy is not needed. But if postmastectomy radiation therapy is required, delayed reconstruction is preferred as it avoids potential radiation delivery problems and generally results in a superior aesthetic outcome. Unfortunately this is often not known until the surgical pathology returns well after the surgery is over.

At the MD Anderson Cancer Center, the “delayed–immediate” protocol is commonly used to answer this conundrum. The protocol is aimed at preserving the breast skin envelope for an optimal aesthetic outcome, while taking into account the possibility that a patient may need to receive adjuvant radiation therapy.

Delayed–immediate breast reconstruction is a two-staged approach. In the first stage, after a skin-sparing mastectomy is performed, a tissue expander is placed until it is known whether or not adjuvant radiation therapy is necessary. Once pathologic review comes back, if radiation is not required, then patients undergo “immediate” reconstruction within weeks with an implant or autologous tissue.

If radiation is required, then the tissue expander is left in place during radiation and delayed reconstruction is performed after the oncologic treatment is finished. Typically, after radiation, breast reconstruction is performed with autologous tissue from the abdomen, back, or thigh to avoid the increased complications associated with implants in a radiated field.

Reconstruction After Partial Mastectomy

In a partial mastectomy, only the portion of the breast that contains the cancer is removed, and the remainder of the breast tissue is left in place. This is performed with the expectation that adjuvant radiation will be required to complete treatment. For some, reconstruction is not required because little or no skin and only a portion of breast tissue is removed during a partial mastectomy. When larger amounts of tissue are removed, the remaining breast tissue can sometimes be “rearranged” subcutaneously to fill the defect. This technique involves mobilizing breast tissue adjacent to the partial mastectomy defect through undermining of the skin over the breast tissue and elevating the breast tissue off of the pectoralis major muscle and then placing deep sutures to eliminate dead space. The skin envelope can also be adjusted in a mastopexy or “breast lift” technique (Fig. 25.3). Collectively, these techniques are referred to as oncoplastic breast reconstruction. If the remaining breast tissue volume is insufficient, additional tissue may be brought to the breast, usually a pedicled or free flap from the back or the abdomen. Immediate reconstruction is preferred in patients who undergo partial mastectomy rather than to performed delayed reconstruction within an irradiated field. Autologous fat grafting, however, may be beneficial following the completion of cancer therapy to

correct any residual volume deficits or contour deformities that remain. Oncoplastic breast reconstruction is an increasingly popular trend that improves the aesthetic outcome following breast-conservation therapy.

Reconstruction After Mastectomy

The majority of breast reconstructions are performed using tissue expanders and implants; latissimus dorsi myocutaneous flaps and implants; or abdominal tissue-based pedicled and free flaps. A staged reconstruction consisting of tissue expansion followed by permanent implant placement is the most common method of breast reconstruction in the United States (Fig. 25.4).

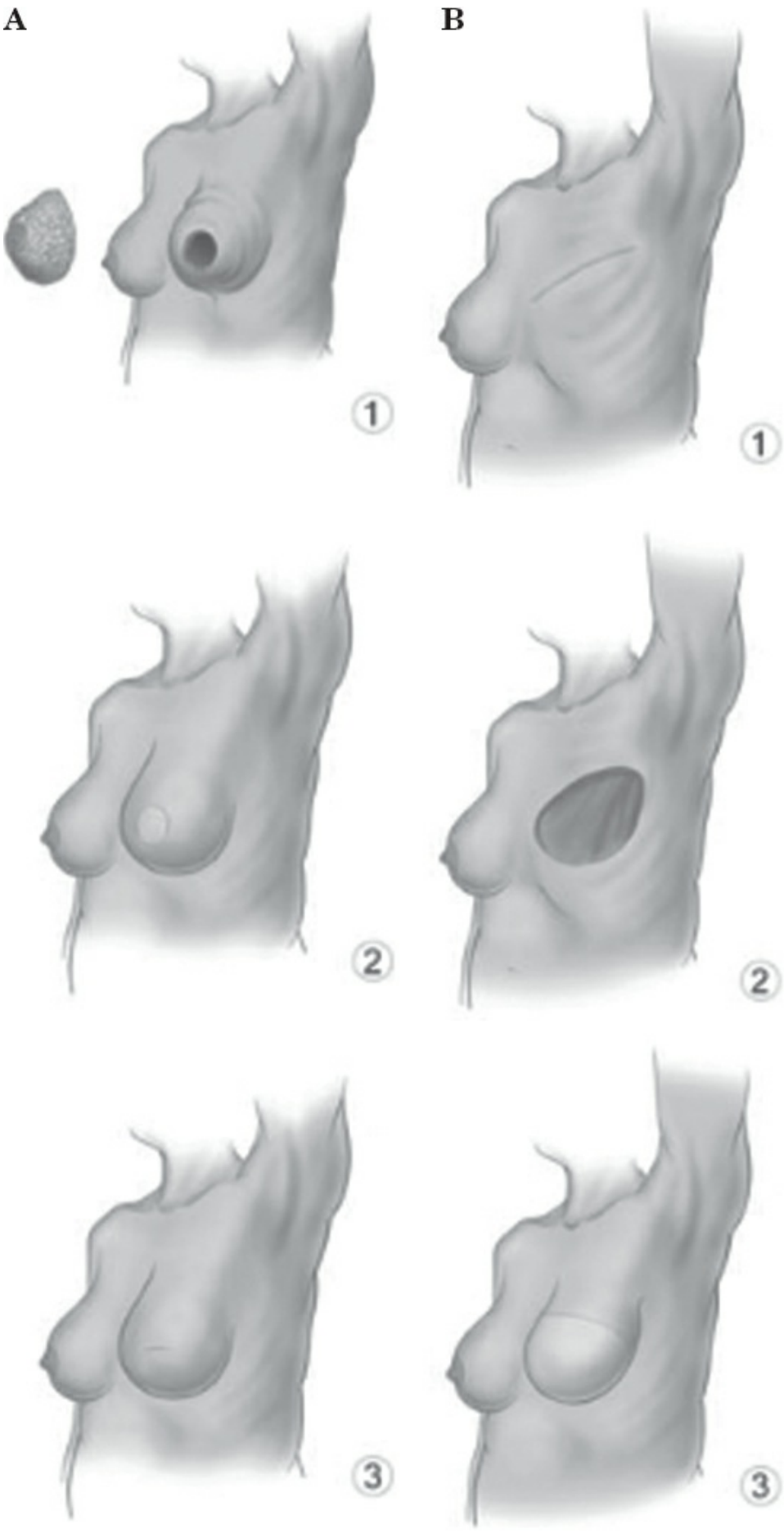
A
B
1
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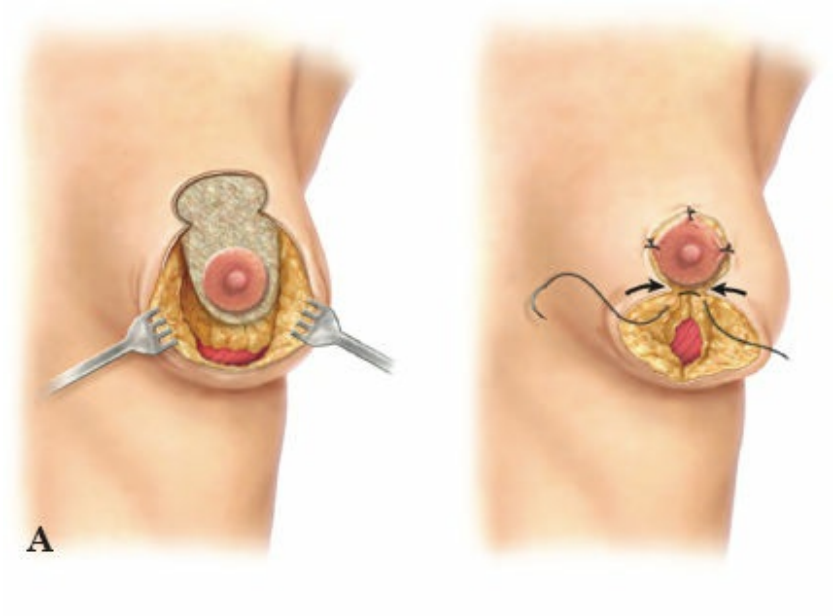
Figure 25.2 Immediate reconstruction (**A**) is performed at the time of the breast cancer surgery. Delayed reconstruction (**B**) is performed after the patient has completed breast cancer treatment.


A

B

C

Figure 25.3 Oncoplastic breast reconstruction involves mobilizing breast tissues to help camouflage a partial mastectomy defect. In cases where the breast is large or ptotic, the skin can be redraped, as in a mastopexy to further minimize the visible defect. **A:** Technique for a typical mastopexy in which the breast tissue is elevated into a less ptotic position and excess breast skin is excised, tightening the skin envelope around the breast parenchyma. (Reprinted with permission from Bland KI, Klimberg VS. *Master Techniques in General Surgery: Breast Surgery*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.) **B:** Preoperative skin markings for a mastopexy. **C:** Postoperative result.

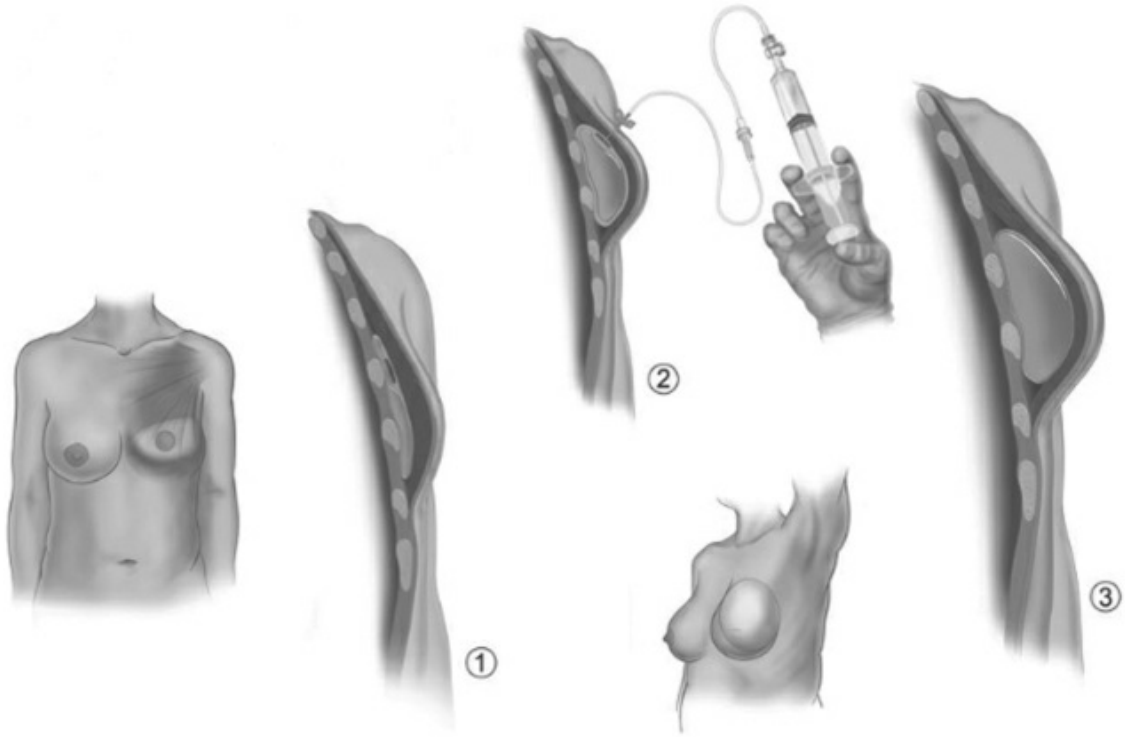


Figure 25.4 Staged breast reconstruction consisting of a tissue expander placed submuscularly followed by permanent implant placement. (**1**) The tissue expander is placed under the muscle followed by serial expansion, (**2**) the tissue expander is replaced with a permanent implant, and (**3**) the unlabeled images reflect pre- and postreconstruction states.

Implant-Based Reconstruction

Implant-based breast reconstruction generally begins with tissue expansion, when an expander is placed under the pectoralis major muscle at the time of mastectomy. The overlying incisions are allowed to heal, and

then saline solution is injected into the expander weekly or every other week until the desired final volume is achieved. After the patient has completed and recovered from all oncologic treatment, a second-stage operation is performed to remove the tissue expander and place the permanent breast implant. Recently, select patients with ideal tissue vascularity and laxity, including patients undergoing nipple-sparing mastectomy, have been reconstructed without tissue expansion, but instead with immediate placement of a permanent breast implant. Early outcomes from “direct-to-implant” patients are promising with respect to complication rates and acceptable aesthetic results.

The advantages of implant-based reconstruction are that it is simple, requires less operating room time than reconstruction with flaps, and is suitable for women who are not able to undergo reconstruction utilizing autologous tissue flaps. The disadvantages of implant-based reconstruction include the potential for infection, capsular contracture, and implant rupture; in addition, young patients may need to undergo implant replacement several times over the course of their lives. Implant-based reconstruction is a poor choice for patients who have received radiation therapy, as it leads to significantly higher risks of seroma formation, infection, capsular contracture, and implant extrusion.

Another type of implant-based reconstruction employs a latissimus dorsi myocutaneous pedicled flap over an implant (Fig. 25.5). The latissimus dorsi is a broad, fan-shaped muscle that originates on the back and inserts into the humerus. Because most women do not have enough tissue volume on their backs for complete breast reconstruction, the latissimus dorsi flap is rarely used alone to reconstruct the breast. Instead, the latissimus dorsi muscle with some of the overlying skin is rotated anteriorly to the chest to cover an implant, facilitate closure of the mastectomy defect (when skin coverage is required) and give the reconstructed breast a more natural contour. The implants used in reconstruction with a latissimus dorsi muscle flap are generally the same as those used after tissue expansion. Some surgeons prefer to use a latissimus dorsi myocutaneous pedicled flap over an implant, because it allows for single-stage breast reconstruction by providing skin to close the areolar or traditional mastectomy cutaneous defect as well as muscle to augment the pectoralis major for full-sized permanent implant coverage. Other surgeons reserve the latissimus dorsi flap for salvage reconstructive cases where a tissue expander or implant has failed due to poor-quality mastectomy skin flaps that necrosed or

dehisced. Finally, latissimus dorsi muscle or myocutaneous flaps are used to cover implants in irradiated mastectomy wounds, providing coverage of the implant with well-vascularized, nonirradiated tissues.

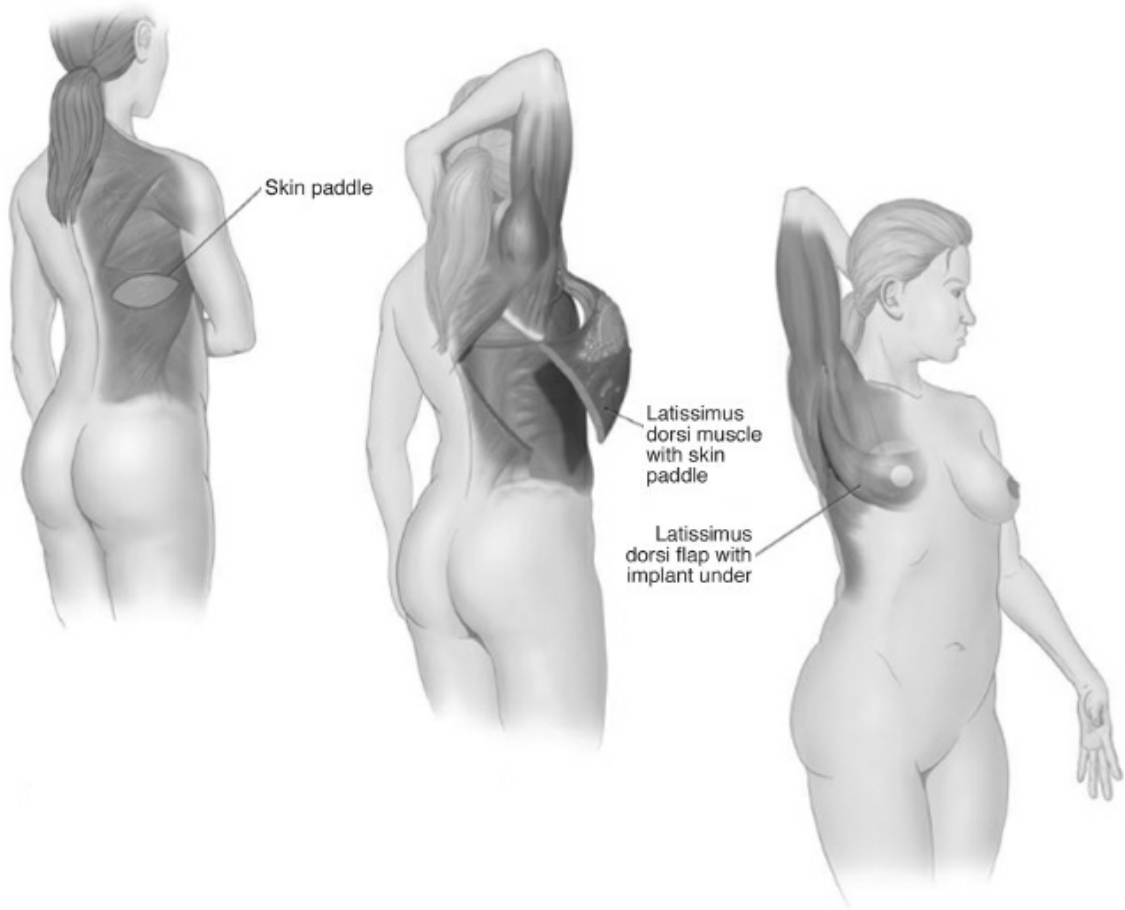


Figure 25.5 The latissimus dorsi muscle flap with skin component (myocutaneous flap). The flap comprising the latissimus dorsi muscle and some of the overlying skin is rotated anteriorly to the chest. An implant can be placed under this flap for appropriate volume reconstruction.

The primary advantage of using the latissimus dorsi flap is that it is a highly vascularized and generally resists infection and protects an implant against extrusion and capsular contracture. Therefore, it can be used as an adjunct in radiated patients to allow implant-based reconstruction. Additionally, in some patients, the skin paddle can provide sufficient tissue to cover the implant without the need for tissue expansion, and thus a staged approach may not be required. The drawbacks of using the latissimus dorsi flap include longer surgery and recovery times than with implant-only reconstructive surgery, a scar on the back, and potential arm adduction weakness following surgery. Regardless, the approach is a

viable option for women who are thin and thus are not candidates for an abdominal flap.

Autologous Tissue Reconstruction

In autologous tissue reconstruction, the patient's own skin, fat, and various amounts of muscle are transferred from one area of the body to the chest to reconstruct one or both breast mounds, usually without the need for a supplemental prosthesis or implant. Autologous reconstruction can be performed as a pedicled flap or a free flap. The most common donor site is the abdomen.

Transverse Rectus Abdominis Myocutaneous Flap

A classic transverse rectus abdominis myocutaneous (TRAM) flap includes the skin and subcutaneous tissue located between the pubic bone and the umbilicus and the rectus abdominis muscle. The flap can be isolated on either the superior epigastric vessels (pedicled TRAM flap) or the deep inferior epigastric vessels (free TRAM flap), as they travel through the rectus muscle (Fig. 25.6).

When used as a pedicled flap, a tunnel is created in the subcutaneous tissue between the abdomen and breast cavities and the flap is passed through this tunnel and rotated into the breast cavity. When used as a free flap, the superior and deep inferior epigastric vessels are divided when the flap is harvested and then the deep inferior epigastrics are reanastomosed to recipient blood vessels in the chest (internal mammary or thoracodorsal vessels) under an operating microscope. The free TRAM avoids several pitfalls of the pedicled TRAM, including an iatrogenic bulge in the upper abdomen and improved fat survival due to better perfusion.

While these TRAM techniques are originally described as taking the entire width of the rectus abdominis muscle, as time has progressed, efforts to take less and less muscle have resulted in several refinements including the muscle-sparing TRAM flap, in which only a small amount of muscle is taken with the blood supply, the deep inferior epigastric artery perforator (DIEP) flap, in which the blood supply is dissected out completely and no muscle is taken with the flap, and the superficial inferior epigastric artery (SIEA) flap (Fig. 25.7).

Other Flaps

Autologous tissue flaps for breast reconstruction can also be harvested

from other sites, including the buttocks or thighs (Fig. 25.8). These flaps are reserved for patients in whom the abdomen is not available as a donor site. Overall, breast reconstruction with autologous tissue produces the best long-term results. However, these procedures are of greater magnitude, are associated with longer operative and recovery times, and have a small (<2% in most high-volume centers) risk of failure.

Nipple and Areola Reconstruction

Nipple–areolar reconstruction, if desired, is performed as a separate procedure after the reconstructed breast has attained its final shape and position. Nipple position on the breast mound is determined based on symmetry with the contralateral breast, and a three-dimensional nipple is constructed with a local skin flap, usually from the breast itself (Fig. 25.9). After the reconstructed nipple has had the opportunity to heal, a "new" areola is tattooed around the reconstructed nipple.

RECONSTRUCTION OF THE TRUNK

The chest and abdominal wall account for roughly one-third of the entire surface area of the human adult body. Surgical defects in the trunk can expose or compromise critical anatomical structures. Additionally, there are dynamic structures that must be able to move and flex with the patient. When possible, oncologic cutaneous defects of the trunk are repaired with wide undermining of the adjacent subcutaneous tissue and local flap advancement. However, when neoplasm resection creates full-thickness defects of the abdominal or chest wall, pedicled or free flaps may be required.

Thorax

Aside from isolated skin cancers, thoracic reconstruction must account for involved pleural cavity, skeletal support (ribs and sternum), and soft tissue coverage of the chest and axilla. Forming an airtight seal at the time of wound closure is crucial to preserving the intrathoracic negative pressure gradient. Skeletal stabilization with prosthetic materials is used to reduce the risk of paradoxical chest wall motion (flail chest) when resections involve four or more rib segments or span more than 6 cm in diameter. Exceptions to this rule include posterior resections underneath the scapula.

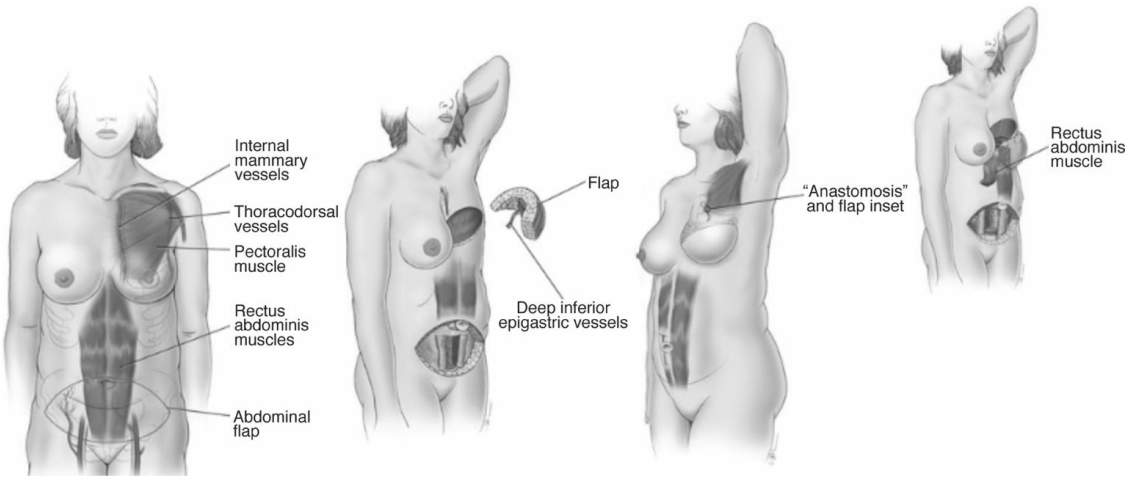


Figure 25.6 The free transverse rectus abdominis myocutaneous flap. This flap is based on the deep inferior epigastric vessels. In breast reconstruction with a free transverse rectus abdominis myocutaneous flap, the deep inferior epigastric vessels are divided at the time of flap harvest and then reattached to recipient vessels (e.g., internal mammary vessels) in the chest under an operating microscope.

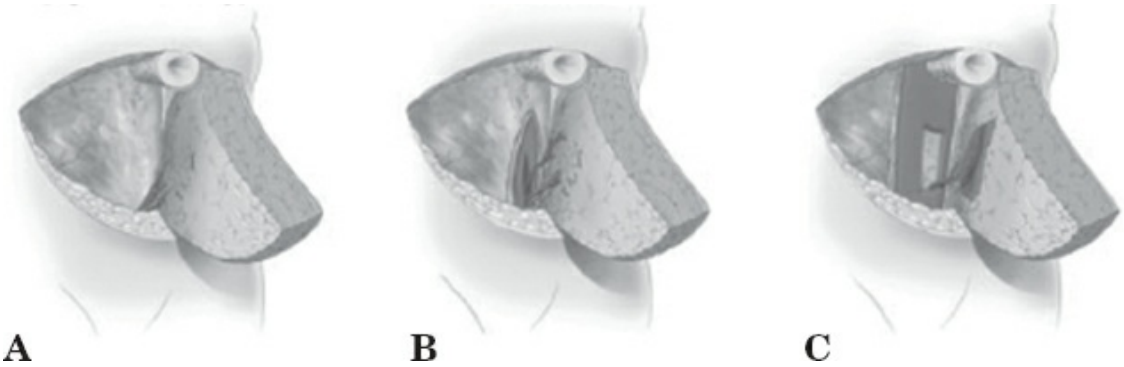


Figure 25.7 **A:** The superficial inferior epigastric artery (SIEA) flap is based on blood vessels that run under the skin and whose harvest does not require dissection into the rectus abdominis fascia or muscle. **B:** The deep inferior epigastric artery perforator (DIEP) flap is based on a dissection of the blood vessels that pass through the rectus abdominis muscle; no muscle or fascia is taken when the flap is harvested. **C:** In breast reconstruction with a muscle-sparing transverse rectus abdominis myocutaneous flap, only a small amount of rectus muscle is taken with the deep inferior epigastric vessels.

The majority of chest wall defects can be repaired with local or regional myocutaneous flaps. Muscle coverage is especially important if there is exposed hardware or prosthetic material. On the anterior chest, the

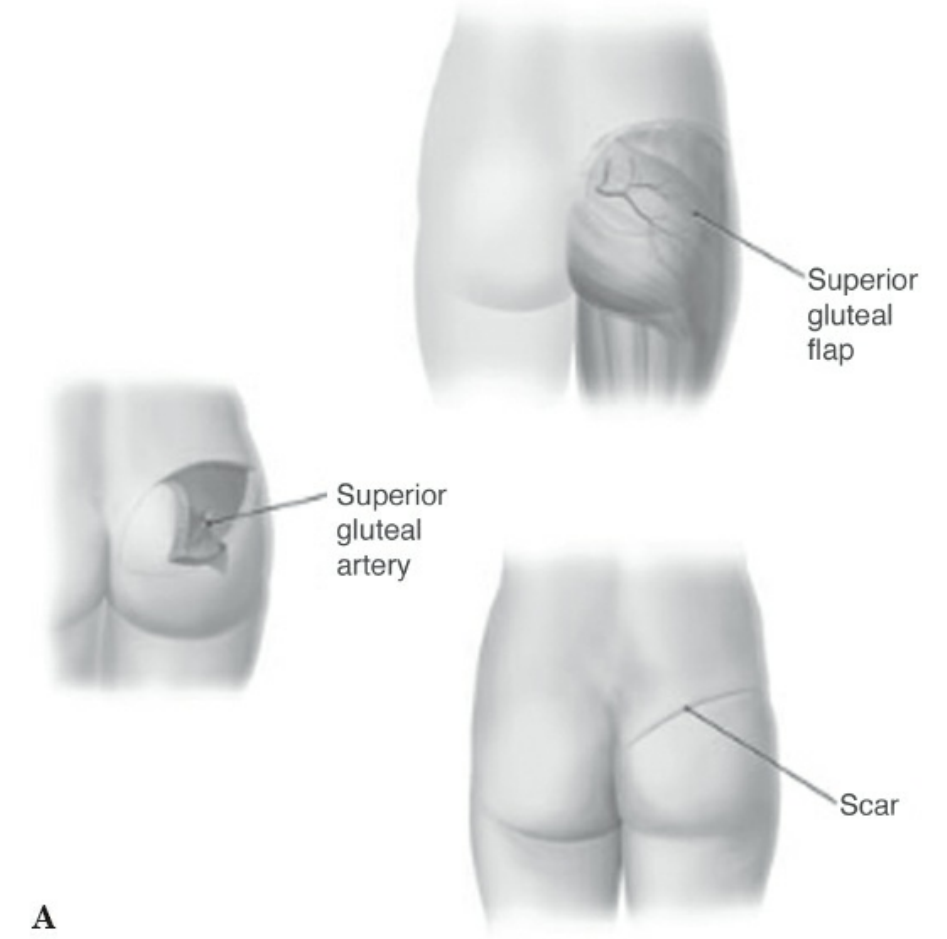
pectoralis major flap is an excellent option for sternal coverage, either as a pedicled flap based on the thoracoacromial vessels or as a turnover flap based on the internal mammary perforator vessels. Additionally, if the mammary vessels are intact, the rectus muscles may be used as rotational flaps for larger defects. Occasionally, the omentum is used when other options are not available. Options for axillary coverage include the pectoralis major and latissimus dorsi flaps. On the posterior thorax, the paraspinous muscles are frequently transposed to cover the spine. Alternatively, the trapezius muscle may be isolated on its vascular pedicle and used to cover the upper spine and cervical region. The latissimus dorsi muscle may also be mobilized on its primary thoracodorsal pedicle or on secondary lumbar perforators as a turnover flap.

Rarely, a free tissue transfer is needed to close oncologic resections of the thorax. In these instances, local options may be unavailable due to radiation damage, pedicle ligation, previous use, or insufficient volume. Free tissue options are then tailored on the exact needs of the defect and may include bone, muscle, and soft tissue.

Abdomen

Most cutaneous defects that result from ablative oncologic surgery in the abdomen can be closed primarily because of the laxity of the skin and subcutaneous tissue in the region. Laterally, the abdominal wall has abundant segmental blood supply from the intercostal vessels and medially it has axial blood supply from the epigastric vessels. In a virgin abdomen, this allows wide undermining and advancement of cutaneous flaps.

If the defect involves the fascia of the abdominal wall, the goal of reconstruction is to restore the integrity and continuity of the abdominal wall. When there is a paucity of fascia, component separation, in which the layers of the abdominal wall fascia and muscle are separated to increase medialization of the rectus components, is often employed. This technique often allows primary closure of the rectus muscle and fascia in the midline while preserving their neurovascular bundles. Laterally, the oblique and transversus muscles are left intact so the entire abdominal wall maintains dynamic contractility. Less commonly, fascial grafts can be taken from tensor fascia lata in the thigh. However, vascularized tissue will always perform better than a graft. A pedicled ALT flap can recruit both fascia and cutaneous elements when other options are scarce.


Superior
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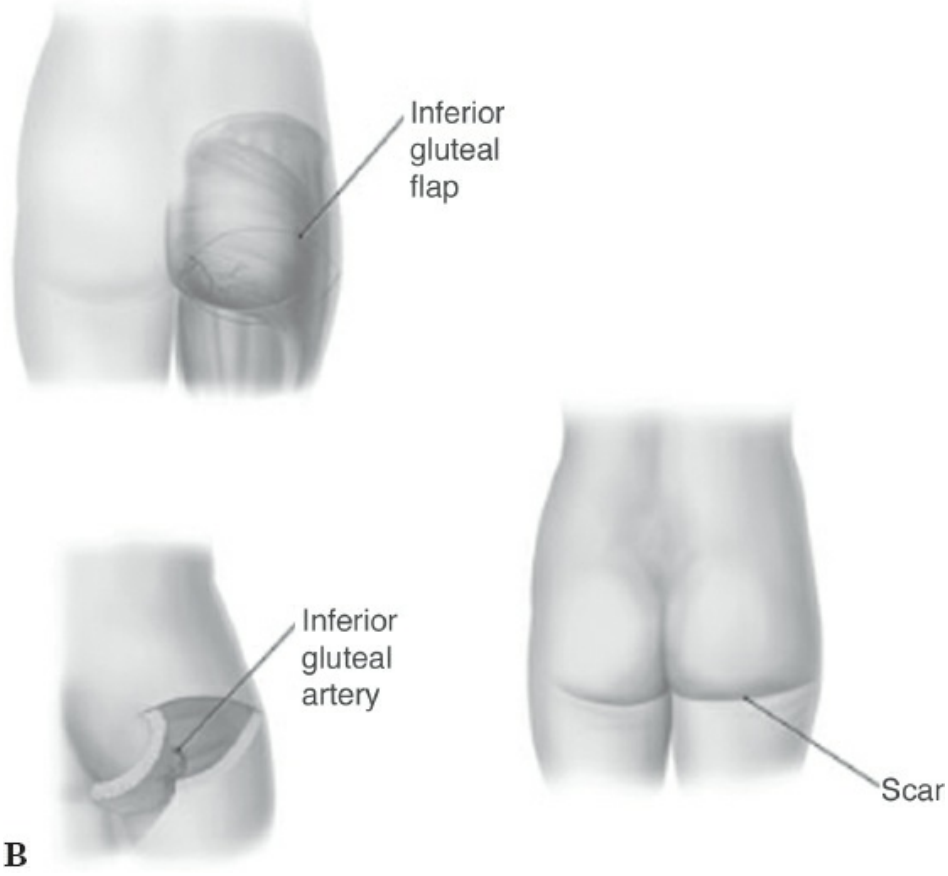
A


Inferior
gluteal
flap
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Scar

B

Figure 25.8 Other flap options for breast reconstruction include the superior gluteal artery perforator flap (**A**) and the inferior gluteal artery perforator flap (**B**).

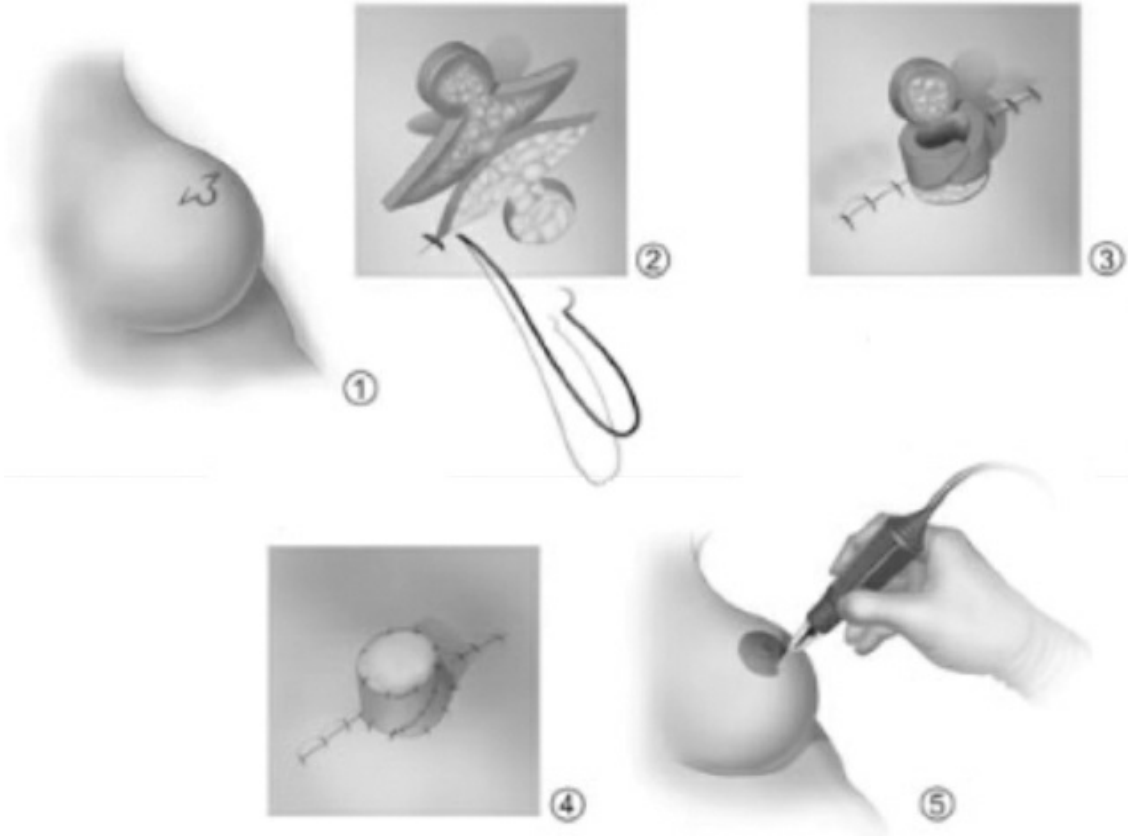

Figure 25.9 Local tissue flaps on the reconstructed breast mound are used to reconstruct the nipple. Outline for skin incision (**1**) a local skin flap is reflected up and folded to reconstruct a three-dimensional nipple (**2**–**4**). Areola pigmentation is performed once the reconstructed nipple has healed (**5**).

In the oncologic patient, adjuvant treatment can decrease abdominal wall strength and healing potential. Often, mesh is used to reinforce abdominal repairs that otherwise would have a high rate of hernia formation. Acellular dermal matrix, a bioprosthetic mesh usually derived from porcine or bovine sources, is often used in an underlay fashion to provide wound strength. Prosthetic meshes can be used in a clean field. Underlay and retrorectus techniques have better long-term outcomes than a bridged repair.

Perineum

Perineal reconstruction presents a unique challenge. The perineum is important for sitting, hip mobility, sexual function, pregnancy, and bowel and bladder motility. Perineal skin and fatty tissue are very sensitive to pressure and touch and are durable, elastic, and weight bearing. In addition, the perineal skin is soft, pigmented, and hair bearing, which makes it challenging to match with distant tissue. The reconstructive discussion and postoperative care is also challenged by strong emotions which may be tied to this area.

Superficial surgical defects of the perineum can be repaired with split-thickness skin grafts, if the wound base is healthy and no vital structures are exposed. Split-thickness skin grafts are especially useful if the status of excision margins is uncertain or the risk of local recurrence is high, as they can be excised and repeated if further resection is required. However, in this dependent area, skin grafts can have a higher risk of failure because of fluid collection below the graft and shear forces.

Local flaps are commonly employed in perineal reconstruction. If the perineum has previously been radiated, or groin dissection has occurred, the area will be prone to seromas, wound dehiscence, and infection. Local flaps bring in healthy tissue to combat this. Small skin defects in the perineum can be repaired with a local rotation flap, such as a rhomboid skin flap. The V to Y random pattern local flap is often used for vulvoperineal reconstruction. Larger defects may require pedicled flaps such as a posterior thigh fasciocutaneous flap or muscle flaps such as a pedicled gracilis flap.

The pedicled vertical rectus abdominis musculocutaneous (VRAM) flap is a workhorse flap for reconstruction of abdominoperineal resections and pelvic exenterations. The rectus muscle is elevated on the deep inferior epigastric vessels with a vertical skin island. The flap is then passed through the pelvic inlet. The muscle can be used for pelvic dead space and the cutaneous portion lines the neoperineum or creates a neovagina. The flap is extremely durable and allows patients to return to baseline activities within weeks. The pedicled ALT flap may also be used for similar indications, including some or all of the vastus lateralis muscle if bulk is needed to eliminate dead space.

RECONSTRUCTION IN THE EXTREMITIES

Multimodality therapy has expanded the indications for limb salvage in patients with cancers of the extremities. Limb salvage, however, must not

be done at the expense of an oncologically adequate resection. In addition, preserving a limb that is nonfunctional, insensate, or painful provides no benefit over amputation. In fact, some patients may do better with prosthesis if rehabilitation is faster. Indications for amputation after extirpative surgery include major neurovascular compromise, significant loss of muscle bulk causing a nonfunctional limb, infection or fractures that compromise reconstruction and delay adjuvant therapy, poor nutrition, serious medical conditions, and a lack of patient motivation or compliance with rehabilitation.

Defects from surgery for soft tissue and bony neoplasms, such as sarcomas, generally require reconstruction with pedicled or free flaps. Neoadjuvant therapy often decreases tumor size and facilitates limb salvage, but radiation therapy may also hinder wound healing and necessitate a nonirradiated tissue flap closure to provide coverage of neurovascular structures, tendons, bone, and endoprostheses.

In limb reconstruction, bony defects can be repaired with prosthetics, allografts, bone grafts, or vascularized bone flaps. Bones may also be temporarily shortened and plated, with later bone-lengthening procedures such as bone transport. Free and pedicled muscle flaps not only provide well-vascularized wound coverage but can also be neurotized to provide functional muscle. Tendon transfers may be performed to allow functioning muscle bellies to take over the function of resected ones. Microsurgical techniques can be used to repair or graft damaged nerves, thereby restoring motor and sensory functions. However, because nerve regeneration occurs at a rate no faster than 1 mm/day, some muscle end plates may die before reinnervation occurs. If reinnervation is expected to take more than 12 to 18 months, some patients may be better served with tendon transfers or amputation.

At a minimum, functional upper limb reconstruction should provide a stable shoulder joint, restore elbow flexion, median nerve sensibility, and prehensile grip. Functional lower limb reconstruction should provide at least stable hip and knee joints, moderate knee flexion, and tibial nerve sensation. This allows the patient to feed and clothe themselves and ambulate with assistive devices. Ultimately, if a limb is amputated, fillet of digit or fillet of arm or leg flaps, can be used as tissue transfers to cover open wounds. In this operation, the uninvolved soft tissue portions of the distal limb are isolated on the neurovascular structures, with the bone removed, and transferred as a pedicle or free flap.

Proximal Arm, Elbow, and Forearm

Proximal arm wounds can be covered with local flaps from the trunk and cervical region. Common flaps include the pectoralis major flap or pedicled latissimus dorsi flap. These flaps can be used to repair defects in the shoulder, axilla, and upper arm. The pedicled latissimus dorsi muscle flap can also be used as a functional muscle transfer to restore elbow flexion or extension in many patients. A common indication for a fillet of arm flap is the forequarter amputation, which includes amputation at the shoulder joint for tumors involving the brachial plexus and axillary vessels.

Soft tissue defects in the elbow and forearm can be reconstructed with a pedicled reverse radial forearm or an ulnar forearm flap. Due to the paucity of muscle bellies in the distal forearm, other local options are scarce. If critical elements are exposed, a free-tissue transfer should be considered. Neurotized latissimus dorsi or gracilis muscle is frequently used for functional muscle belly reconstruction. If bone is required, free vascularized grafts from the fibula or scapula are options.

Hand

The hand is one of the most specialized and ergonomically efficient structures in the body. Comprised mostly of bone, tendon, nerves, and skin, the hand is a compact structure with unparalleled motor and sensory function. Because the hand is crucial to the functions of everyday life, a baseline functional assessment should be performed before tumor excision.

The scope of hand reconstruction is outside the limits of this text and subspeciality of its own. However, certain principles apply throughout. For example, glabrous skin on the palm and fingers is highly specialized and should be repaired by primary closure whenever possible. Skin grafts from the contralateral palm or plantar foot may be the best match if this is not possible. Some sensation, especially at the fingertips, is better preserved by secondary healing than replacement with an alternate tissue. The skin of the dorsum of the hand is thin with moderate laxity and may be replaced with similar tissue from another area, such as the groin.

As a general principle, digit length should be preserved to the greatest extent possible during oncologic resection. This allows proper function of the extensor and flexor tendons, which function like a pulley system and require a fine balance. The tendons of the hand are surrounded in

vascularized paratenon and every effort should be made not to strip them of this covering, as it can lead to necrosis or rupture. If they are stripped by tumor resection, they should be covered by vascularized tissue, even a free flap if necessary. Bone grafts can be used to replace phalangeal and metacarpal resections. When amputation is necessary, it is generally performed through the most distant joint possible.

When neural structures are involved, primary nerve repair or a nerve graft may be used to preserve adequate function. Epineurial or interfascicular repairs are also typically performed depending on the nerve and location. Small sensory branches can be spared from the extremities and make useful grafts. A commonly harvested nerve is the sural nerve from the lower leg.

Lower Extremity

Oncologic extirpation in the lower extremity can result in defects of the groin, thigh, knee, lower leg, and foot. The most common tumor in the lower extremity is sarcoma.

When defects occur in the groin or thigh, many times they can be closed by pedicled flaps. The most common flaps in this region are a pedicled rectus abdominis myocutaneous flap or an ALT flap. After groin dissection, the proximal femoral vessels are often exposed and the neighboring sartorius muscle can be transposed for coverage. With massive defects of the thigh, free tissue transfers can be performed and the femoral and deep femoral vessels are usually good recipients. End-to-side anastomoses are commonly performed in the lower extremity to preserve blood flow to the distal limb.

In the knee and leg, many defects are associated with osteotomies associated with tumor resection. Bony defects in the distal femur and proximal tibia are usually reconstructed with an allograft or endoprosthesis. Soft tissue coverage of defects in the knee and proximal one-third of the lower leg can be achieved with pedicled gastrocnemius muscle flaps. The medial or lateral heads of the gastrocnemius can be separated and used as individual pedicled muscle flaps, or both heads can be used to provide more coverage. If both heads of the gastrocnemius muscle are to be used for reconstruction, the soleus muscle must be preserved to provide plantar flexion of the foot. Alternatively, when soft tissue coverage is required in the middle third of the leg, the soleus muscle can be used as it has better reach in this area.

In comparison to the more proximal thigh and leg, reconstructing the distal third of the leg with local or regional muscle flaps is not usually possible because of sparse amount of local tissues available. In the distal third of the leg, most muscle bellies have become tendinous and tightly fixed to the bone. Generally, all but the smallest wounds in this region must be repaired with free fasciocutaneous, or myocutaneous free flaps. Three sets of vessels are present in the lower leg—the anterior tibial, posterior tibial, and peroneal vessels. Any of these can be suitable for free flap anastomosis. The lower leg and foot can survive off a single vessel if necessary, although it is preferable to leave at least two systems intact.

Foot

Like the hand, the foot is extremely specialized. It bears the entire weight of the body and therefore must have extremely durable coverage. Additionally, it must have fine sensation to protect against frequent trauma and infection. Because of this, sacrifice of the tibial nerve during tumor extirpation and subsequent rendering of the plantar foot insensate, is a hard indication for amputation with few exceptions.

Similar to the hand, very small oncologic resections are best repaired with primary closure or secondary healing. Small defects can be repaired with skin grafts and local flaps. Due to the paucity of muscle and soft tissue in the lower leg, there are few local flaps available for foot reconstruction. The reverse sural artery rotation flap can repair small defects at the heel or malleolus. The medial plantar artery flap includes the glabrous skin of the instep and can be moved short distances from the non–weight-bearing area of the foot to the weight-bearing surface. However, both these flaps are limited in their reach.

When defects reach over 5 cm, they must be repaired with a free flap. Smaller but durable muscles such as the gracilis or serratus anterior can be used and then covered with a skin graft. Fasciocutaneous flaps such as the radial forearm flap are also used for foot reconstruction and can be designed to include sensory innervation. Insensate muscle and fasciocutaneous flaps are susceptible to pressure ulceration and so must be vigilantly monitored for the breakdown of skin and soft tissue. Care must be taken when planning free flaps for the foot, as being able to wear a shoe is exceedingly important in the activities of daily life. Bulky flaps are usually unfavorable for ambulation and may necessitate revision surgery and/or special orthotic footwear.

SUMMARY

Reconstruction for oncologic defects requires attention to both aesthetic and functional requirements. These defects can be routinely and safely reconstructed using multidisciplinary and systematic approaches while always being cognizant of following oncologic principles. The ultimate goal of reconstructive surgery is a healed wound with minimal patient morbidity. Coordinated and specialized reconstructive techniques optimize aesthetic and functional outcomes.

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