Gynecologic Oncology Handbook

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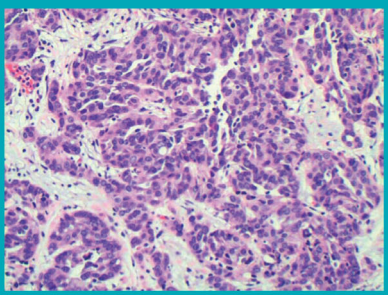

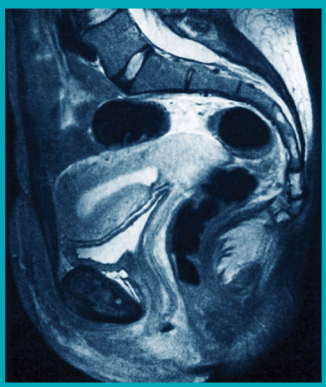

AN EVIDENCE-BASED CLINICAL GUIDE

Michelle F. Benoit
M. Yvette Williams-Brown
Creighton L. Edwards

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Gynecologic Oncology Handbook

An Evidence-Based Clinical Guide

Second Edition

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The second edition is dedicated to our mentor and friend, Dr. Creighton Edwards, an outstanding clinician, educator, and role model. He taught us to treat the whole patient, to stand up for what is right, and gave us the resolve to always keep trying. He is our John Wayne of medicine: he showed us that "courage is being scared to death but saddling up anyway."
—Michelle and Yvette

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Preface

This handbook is structured to provide comprehensive care for the gynecologic cancer patient. It is directed toward clinicians at all levels of training and the chapters are tiered in this fashion. Basic diagnosis, workup, staging, and treatment are outlined first. Specific surgical and adjuvant therapies are then recommended reflecting the most current standards of care. Finally, the evidence-based medicine is summarized in support of recommended treatments. Thus, the medical student can have a dedicated overview, the resident can refer to directed patient care protocols, and the fellow and practicing physician can support their clinical decisions with easily accessible literature.

The updated second edition furthers the content to include: the latest cancer-screening information, new surgical technology and platforms, novel cytotoxic chemotherapy in addition to targeted and immunotherapy treatments, vaccination information, and the most current clinical trial outcomes. The 8th Edition AJCC staging guidelines have also been incorporated, providing accurate instructions for staging to keep the reader at the forefront of medicine. With this additional information, we provide a comprehensive and contemporary reference for clinical practice.

It continues to be our honor to assemble this handbook for our friends and colleagues. We again acknowledge the dedication it has taken from the physicians, support staff, and especially our patients, to design and participate in the trials that have advanced our knowledge of these difficult gynecologic cancers. In particular, we would like to acknowledge Hong Xiu Ji, MD, PhD, and Mr. James Romnes, PA, for providing the histology images. We hope the information provided herein can continue to guide high-quality care and reflect our commitment to the subspecialty.

Michelle F. Benoit, MD
M. Yvette Williams-Brown, MD, MMS
Creighton L. Edwards, MD

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GYNECOLOGIC CANCERS 2

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Cervical Cancer

CHARACTERISTICS

There are approximately 400,000 new cases of cervical cancer worldwide annually. In 2017 there were 12,820 anticipated new cases identified with approximately 4,210 deaths in the United States.

- The most common symptom of cervical cancer is abnormal vaginal bleeding—specifically, postcoital and intermenstrual bleeding, menorrhagia, and postmenopausal bleeding. Other symptoms include pelvic fullness/pain, unilateral leg swelling, bladder irritability, and tenesmus. Cervical cancer is also commonly asymptomatic, found only following an abnormal Pap smear, colposcopic exam, or cervical biopsy.
- Common signs of advanced cervical cancer are a fungating cervical mass, unilateral leg edema, and obstructive renal failure.
- Cervical cancer often results from persistent infection with high-risk HPV types (most commonly 16 and 18). Risk factors associated with cervical cancer are: prior history of sexually transmitted diseases (STDs), early age of first coitus, multiple sexual partners, multiparity, nonbarrier methods of birth control, and smoking.
- Cervical cancer primarily spreads by direct extension from the cervix to the parametria, vagina, uterine corpus, and the pelvis. Other routes of spread include lymphatic and hematogenous dissemination, as well as direct peritoneal seeding.
- Lymph node (LN) metastasis usually occurs in a sequential fashion, traveling first to the parametrial LNs, then to pelvic (obturator, internal, and external iliac), common iliac, para-aortic, then scalene LN.

PRE-TREATMENT WORKUP

The pre-treatment workup of cervical cancer begins with a history and physical exam. Laboratory studies to assess hematologic, renal, and liver functions should be performed. Imaging studies should also be performed to include pelvic imaging and a CXR (Figure 2.1).

- FIGO-approved imaging studies include barium enema, intravenous pyelogram, and chest x-ray. Other modalities such as CT (to assess LNs and evaluate for hydronephrosis), MRI (to assess integrity of tissue planes and extent of cervical disease), or PET/CT (to evaluate for distant metastasis) are non-FIGO-approved staging tests due to the poor availability of these imaging modalities in medically underserved countries. However, advanced imaging is important in depicting important prognostic factors and, when available, is recommended in addition to the clinical examination.
- Cervical conization should be used to evaluate microscopic disease. Conization can differentiate between microinvasive versus invasive early-stage disease.

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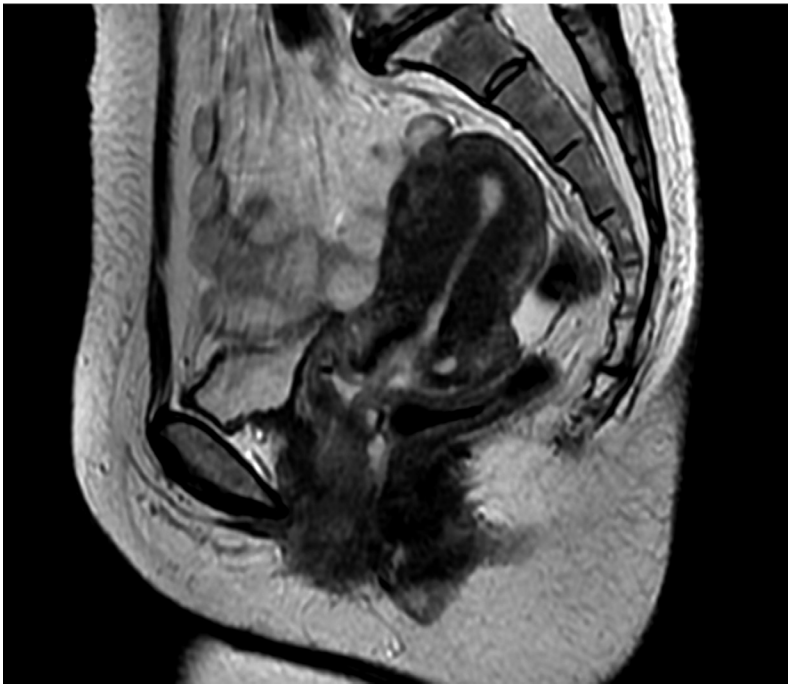

Figure 2.1 MRI of stage IIB squamous cell cervical cancer.

- For lesions that are macroscopic, an office examination or an examination under anesthesia (EUA) with cystoscopy and proctoscopy is indicated.
- If patients cannot tolerate an office exam, or if there is ambiguity about the staging in an office setting, an EUA should be performed. There are data to suggest that EUA can significantly change clinical staging: 23% were upstaged, most to IIA or IIB disease. Patients were down staged less often (9%) to IB2 and IIB. Proctoscopy was not found to be helpful, but cystoscopy identified 8% of patients with stage IVA disease, and a CXR was abnormal in 4% of patients (1).
- Multiple studies have supported the use of PET scans. An analysis of 15 published (FDG)-PET studies on cervical cancer showed that the pooled sensitivity and specificity of FDG-PET for detecting pelvic LN metastasis were 79% (95% CI: 65%–90%) and 99% (95% CI: 96%–99%), compared with 72% (95% CI: 53%–87%) and 96% (95% CI: 92%–98%) for MRI, and 47% (95% CI: 21%–73%) for CT (specificity not available). The pooled sensitivity and specificity of FDG-PET for detecting PA-LNs were 84% (95% CI: 68%–94%) and 95% (95% CI: 89%–98%) (2). A study from Israel (3) revealed a sensitivity of 60%, a specificity of 94%, a PPV of 90%, and an NPV of 74%. PET–CT may not pick up lesions smaller than 1.5 cm. There are data to suggest that treatment modification can occur in 25% of patients based on PET–CT results.

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HISTOLOGY

There are several different histologic types of cervical cancer, the most common being squamous (85%). Other types include adenocarcinoma (15%–20%), verrucous carcinoma, adenosquamous carcinoma, clear cell carcinoma, neuroendocrine carcinomas, and undifferentiated types.

- Adenocarcinoma: about 15% have no visible lesion because the lesion arises from the endocervical canal, forming a "barrel-shaped" lesion. Cells frequently stain CEA+. Variants are the more common mucinous endocervical, mucinous intestinal type, signet ring type, and colloid variants. Adenoma Malignum/Minimal Deviation Variant has an infiltrative pattern distinct from those listed elsewhere with cytologically benign appearing cells on low power but moderate nuclear atypia seen on higher power and are seen in patients with Peutz–Jeghers syndrome. There is a three-tiered system developed to classify risk of LN metastasis developed by Silva et al. (4).
  - Pattern A: well-demarcated glands frequently forming clusters or groups with lobular architecture and lacking destructive stromal invasion or LVI. LN metastasis risk: 0%.
  - Pattern B: localized destructive invasion with small clusters or individual tumor cells within desmoplastic stroma often arising from pattern A glands. Often well to moderately differentiated. LVI ±. LN metastasis risk: 4.4%.
  - Pattern C: diffusely infiltrative glands and associated desmoplastic response. Confluent growth filling a 4× field (5 mm) or mucin lakes present, solid poorly differentiated component with LVI. LN metastasis risk: 23.8% (5).
- Verrucous carcinoma: this is a well-differentiated squamous cell carcinoma. It is known to recur locally, but does not metastasize. Historically, these tumors should not be treated with radiation therapy (XRT) because radiation can cause anaplastic transformation; however, recent evidence does not support this. It is associated with HPV6.
- Adenosquamous carcinoma: this is a mixed glandular and squamous carcinoma. It behaves similar to adenocarcinoma.
- Glassy cell carcinoma: this is a poorly differentiated type of adenosquamous carcinoma.
- Clear cell carcinoma: this is a poorly differentiated carcinoma. It is nodular and reddish in gross appearance. It has a hobnail cell shape microscopically. It can be associated with intrauterine DES exposure.
- Neuroendocrine carcinoma: this includes the small cell, large cell, and carcinoid (typical and atypical) carcinomas. Small cell is the most common neuroendocrine tumor in the cervix. It contains adenoid basal cells with scarce myoepithelial differentiation.
- Papillary squamous cell: this is a variant of squamous cell carcinoma. It appears as transitional or cuboidal cells on microscopy.
- Mesonephric adenocarcinoma: remnants of the mesonephric ducts are occasionally seen in the lateral aspects of the cervix, are PAS+, and do not contain intracytoplasmic mucin (Tables 2.1A–D and 2.2).

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Table 2.1A AJCC 8th Edition and FIGO 2009: T Category

T	FIGO	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA2	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even with superficial invasion
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus such as the vagina, but not the pelvic wall or to the lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor has spread to the parametrial area.
T3	III	Tumor extending to the pelvic sidewall and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic sidewall
T3b	IIIB	Tumor extending to the pelvic sidewall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

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Table 2.1B AJCC 8th Edition and FIGO 2009: N Category

N	FIGO	N criteria
NX		Regional LNs cannot be assessed
N0		No regional LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) not greater than 0.2 mm
N1		Regional LN metastasis

LN, lymph node.

Table 2.1C AJCC 8th Edition and FIGO 2009: M Category

M	FIGO	M criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant LNs; lung; liver; or bone)

LN, lymph node.

Table 2.1D AJCC 8th Edition and FIGO 2009: Stage Grouping

When T is	And N is	And M is	Then the stage group is
T1	Any N	M0	I
T1a	Any N	M0	IA
T1a1	Any N	M0	IA1
T1a2	Any N	M0	IA2
T1b	Any N	M0	IB
T1b1	Any N	M0	IB1
T1b2	Any N	M0	IB2
T2	Any N	M0	II
T2a	Any N	M0	IIA
T2a1	Any N	M0	IIA1
T2a2	Any N	M0	IIA2
T2b	Any N	M0	IIB
T3	Any N	M0	III
T3a	Any N	M0	IIIA
T3b	Any N	M0	IIIB
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

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Table 2.2 Cervical Cancer Overall Survival by Stage

Stage	5Y survival (%)
IA	93
IB	80
IIA	63
IIB	58
IIIA	35
IIIB	32
IVA	16
IVB	15

TREATMENT

The treatment of cervical cancer may involve the use of surgery, chemotherapy, radiation therapy (XRT) or a combination of therapies. About 70% of newly diagnosed patients with invasive carcinoma of the cervix have disease limited to the uterine cervix and are, therefore, potential operative candidates. 54 to 84% of these patients will need adjuvant therapies for intermediate or high-risk factors; so thorough investigation of the full extent of disease should be performed. NCI statements support treatment with the fewest number of interventions; thus, if high-risk factors are found on conization, which predict a high probability for the need of adjuvant therapies, it may be prudent to not perform surgery.

- Treatment options by stage:
  - Stage IA1:
    - No LVSI: a simple (type I/extrafascial) hysterectomy or cold knife cone with 3 mm negative margins (if fertility-sparing treatment is desired) are adequate therapies. Intracavitary XRT can be used alone if the patient is not a surgical candidate. If margins on the CKC are positive, repeat CKC should be performed. Consideration of simple trachelectomy if fertility is desired is another option. If margins continue to be positive for carcinoma, a type II radical hysterectomy with pelvic LND can be considered.
    - LVSI: a type II (modified) radical hysterectomy with pelvic LND (P-LND) with/without para-aortic LND should be considered. Whole pelvic (WP) external beam XRT (EBXRT) with brachytherapy can also be considered. If fertility is desired, a cone biopsy with negative 3 mm margins with a pelvic LND, and consideration of para-aortic LND (PA-LND) should be performed. A radical trachelectomy with pelvic LND can also be considered.
  - Stage IA2:
    - A type II or type III radical hysterectomy with P-LND with/without PA-LND can be offered. Similar outcomes have been seen with both types of radical hysterectomy (6) or
    - Pelvic EBXRT with brachytherapy

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- Stages IB1 and IIA1:
  - A type III radical hysterectomy and pelvic LND with/without PA-LND can be offered with consideration of SLN mapping. Surgical candidates are those with lesions that are not bulky or barrel shaped.
  - Definitive treatment can also be primary external beam radiation therapy (EBXRT) and brachytherapy with concurrent cisplatin chemotherapy. Total dosing for XRT should be 80–85 Gy. Similar cure rates are seen with either radical surgery or XRT (7).
- Stages IB2 and IIA2:
  - A combination of EBXRT and brachytherapy with chemotherapy is the standard of care. Patients with large cervical lesions staged IB2 have a high rate of needing adjuvant therapies after surgical approach and primum non nocere states the least injurious approach be the standard of care. Total dosing with XRT should be ≥85 Gy.
  - A type III radical hysterectomy with P-LND with/without PA-LND can be considered.
  - Surgical LN staging can be considered via extraperitoneal or transperitoneal laparoscopic LND. If negative, tailored field EBXRT and brachytherapy with concurrent cisplatin chemotherapy can be administered. If positive, then the need arises for EBXRT to cover the para-aortic and involved LN basins.
  - Surgery can be considered as adjuvant therapy in certain situations; for example, if there is residual tumor after definitive chemotherapy–XRT or uterine anatomy precludes adequate brachytherapy. Total dose with this approach is 75–80 Gy.
- Stage IB2, IIA2, IIB, IIIA, IIIB, IVA: CT of chest, abdomen, and pelvis should be obtained:
  - If imaging shows adenopathy:
    - Positive pelvic adenopathy but negative PA adenopathy: consider laparoscopic LND of pelvic and PA basins or fine needle aspiration (FNA) of suspicious LN:
      - If positive PALN: WP EBXRT and brachytherapy with extended field XRT concurrent with cisplatin chemotherapy.
      - If negative PALN: then WP EBXRT with brachytherapy concurrent with cisplatin chemotherapy (tailored fields).
    - If no surgical LN evaluation is performed: WP EBXRT with brachytherapy concurrent with cisplatin chemotherapy with/without extended field para-aortic (PA-XRT) can also be considered.
    - Positive pelvic and PA adenopathy on imaging: consider laparoscopic LND followed by WP and PA EBXRT to affected LN basins with brachytherapy, concurrent with cisplatin chemotherapy.
    - If distant metastases are seen: systemic chemotherapy with individualized palliative XRT.
- Stage IVB: chemotherapy should be used for disseminated disease and XRT can be considered for pelvic tumor control or palliation of symptoms including bleeding.

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- If cancer is incidentally found on a postoperative hysterectomy specimen:
  - Stage IA1 with LVSI or >stage IA2: imaging should be obtained with pathologic review:
    - Negative margins and negative imaging:
      - WP EBXRT and brachytherapy with concurrent cisplatin chemotherapy should be offered or
      - A parametrectomy with upper vaginectomy and P-LND with/without PA-LND can be performed
    - Positive margins or gross residual disease:
      - If imaging is negative for adenopathy: WP EBXRT with concurrent cisplatin chemotherapy with/without brachytherapy based on vaginal margins
      - If imaging is positive for adenopathy: consider debulking of grossly enlarged LN followed by WP and PA EBXRT with concurrent cisplatin chemotherapy with/without brachytherapy based on vaginal margins

- Most randomized trials included 5% to 8% of patients with adenocarcinoma, so they are applicable to cite in treating adenocarcinoma of the cervix.
- Margin status is important in conization. In one study evaluating adenocarcinoma in situ (8), 33% of patients with negative margins had residual disease at the time of hysterectomy and 14% had invasive cancer; 53% of those with positive margins had residual disease and 26% were found to have invasive cancers. In another study, which reviewed patients with invasive squamous cell cancer on conization (9), 24% of patients had residual disease if they had negative margins and 60% were found to have residual disease if they had positive margins.
- The incidence of positive LNs with squamous cell and adenocarcinomas is 5% for stage IA2, 15% for stage IB1, 30% for stage IB2, 45% for stage IIB, and 60% for stage IIIB.
- The incidence of adnexal metastasis with adenocarcinoma is 1.7% compared to 0.5% for squamous cell lesions. According to GOG 49 (10), this is a nonsignificant difference, and all patients with ovarian metastasis had evidence of other extra-cervical disease.
- The rate of an aborted radical hysterectomy for grossly positive LNs is approximately 7% to 8% (11). Per GOG 49, the rate of abandoned radical hysterectomy was 8.3%.
- If a positive LN is found at the time of radical hysterectomy, there are two management options: completion of, or abortion of, radical hysterectomy.
  - Some proceed and complete the radical hysterectomy. The rationale is that removal of bulky LNs leaves less residual tumor for XRT to sterilize.
  - Another study showed that the local recurrence and distant recurrence rates were not significantly different for LN positive aborted versus completed radical hysterectomy patients. The progression-free survival (PFS) was 74.9 months versus 46.8 months ($p = 0.106$) and the overall survival (OS) was 91.8 months versus 69.4 months ($p = 0.886$) (12). Potter (13) found similar outcomes and the trend favored definitive XRT. Leaving the uterus in situ can help with treatment planning and can move the small bowel out of the treatment field. Debulking of LN greater than 2 cm prior to abortion of hysterectomy may be beneficial additionally.

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  - The number of positive LN affects OS. The 5-year survival (YS) decreases for each additional positive LN: 1 node (79%), 2 to 3 nodes (63%), 4+ nodes (40%) (14).
- Surgical staging in locally advanced cervical cancer may be beneficial. In one study, surgical staging of women with locally advanced cervical cancer was suggested to improve overall clinical outcome, as those with positive LNs had a modification in standard XRT fields in up to 43% of patients (15).
- LN debulking can potentially improve the 5 YS in patients with locally advanced cervical cancer (16). One study showed that if grossly metastatic LNs were resected, the survival of women in that group approached the level of those women who had microscopic LN involvement only (50%, 5 YS), which was significantly higher than the women with unresectable LNs (0%) (16). There was a 10.5% incidence of severe XRT-related morbidity and a 1% incidence of treatment-related deaths due to combined therapies.
- A cut through hysterectomy refers to a cancer either found incidentally on final pathology or resected without radical surgery. Treatment of a "cut through" can include adjuvant XRT or a radical parametrectomy. There are data to suggest that the 5 YS is better with adjuvant XRT versus radical parametrectomy with a 68.7% versus a 49% 5 YS. This is stage and margin dependent. The 5 YS for women staged IA2 and IIA was 96% (17), but was much lower for women stage IIB or higher who had a 5 YS of 28%.
- Hydronephrosis found on imaging predicts a worse OS and PFS. Relief of ureteral obstruction has been associated with improved survival. Management with stenting via cystoscopy from below, or antegrade from above, is beneficial for preservation of renal function and enabling full dosing of radiosensitizing chemotherapy (18).

SURGICAL TREATMENT

- Hysterectomy types: Piver classification I–V is based on the degree of resection of vagina, parametria, cardinal ligaments, and uterosacral ligaments (19).
  - Class I radical hysterectomy is the same as a simple hysterectomy. It is indicated for stage IA1 cervical cancers without lymphovascular space involvement.
  - Class II radical hysterectomy is a modified radical hysterectomy. It involves resection of the medial half of the cardinal and uterosacral ligaments. The uterine artery is taken at its junction with the ureter. The upper one fourth (or 1–2 cm) of the vagina is also removed. This results in a wider local treatment margin than a simple hysterectomy.
  - Class III radical hysterectomy is also called a Wertheim/Meigs–Okabayashi hysterectomy. Originally, Wertheim did not include lymphadenectomy, whereas Meigs and Okabayashi did. In this procedure, the cardinal and uterosacral ligaments are completely transected and one third to one half of the vagina is removed. The uterine artery is taken at its origin. The autonomic nerves for bladder and rectal function are also resected, which can result in a high incidence of prolonged or permanent bladder dysfunction (Figure 2.2).
  - Class IV radical hysterectomy is reserved for larger bulky lesions. This procedure involves completely transecting the cardinal and uterosacral ligaments at their origin. One half of the vagina is removed; therefore, sexual

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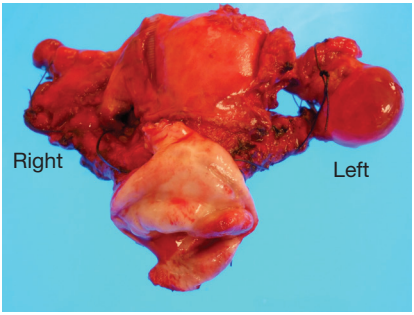

Figure 2.2 Type III radical hysterectomy.

dysfunction occurs from the shortened vagina. The superior vesical artery is sacrificed and all periureteral tissue is removed.
    - Class V radical hysterectomy is reserved for tumors that invade to the lower urinary tract. It involves the removal of involved portions of the bladder as well as the distal ureters.
- There are data to suggest for early-stage (IB–IIA) cervix cancer that there is no difference in recurrence rate or survival rate between class II or III radical hysterectomy. Surgeries took longer for the type III hysterectomies (6).
- A scalene LND is done if there is a question about distant metastasis. There are data to suggest that 10.7% of patients with positive para-aortic LNs have positive scalene nodes. PET scanning may be a reasonable alternative to a scalene LND (20).
    - The boundaries of the neck are the anterior and posterior triangles.
        - The anterior triangle is bordered by the sternocleidomastoid, the mandible, and the midline of the neck.
        - The posterior triangle is bordered by the sternocleidomastoid, the clavicle, and the trapezius. This is the larger triangle of the neck in which the scalene triangle lies.
        - The boundaries of the scalene triangle are the inferior belly of the omohyoid muscle, the sternocleidomastoid, and the subclavian vein. The scalenus anterior muscle lines the floor of the triangle. The phrenic nerve runs through the scalene triangle, as does the thoracic duct. If the duct is transected, it must be ligated at both ends to prevent a fistula.
- Other surgical techniques and indications:
    - Radical vaginal hysterectomy (Schauta–Amreich procedure) is performed in two stages. The first stage involves a retroperitoneal pelvic LND, most commonly via laparoscopy. The second step is to perform a vaginal radical hysterectomy.
    - Laparoscopic radical hysterectomy: this can also be approached with robotic assistance.
    - Radical trachelectomy:
        - This procedure is indicated in patients who desire fertility with tumors that are stage IB1 or lower, low grade histology, and that are less than 2 cm in maximum diameter. There are some feasibility data for tumors up to

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4 cm. Of note, 60.7% of these patients had adjuvant therapies based on pathologic high pathologic risk factors to include XRT, chemotherapy, or both (21). Care should be taken with the larger and more aggressive histologic types. Neuroendocrine and adenoma malignum histologies fall into this category. Please refer to Chapter 6 for further fertility discussion.

  - A radical trachelectomy involves the radical dissection and removal of the uterine cervix. This can be performed by either an abdominal, laparoscopic (with robotic assistance) or via the Schauta–Amreich vaginal approach. The cervix is amputated from the uterine corpus about 1 cm below the isthmus. An ECC is performed and sent for frozen pathology. If the ECC is positive, the radical hysterectomy is performed. If it is negative, a McDonald's or Shirodkar cerclage is usually placed at the time of surgery due to the risk of preterm labor from creating a shortened cervix. A Saling procedure, which advances the vaginal mucosa to cover the external os, can be performed at 14 weeks intrauterine pregnancy to reduce the risk of ascending infection. A separate LND can be accomplished via extraperitoneal laparoscopic or transperitoneal laparoscopic approaches. Only the parametrial nodes can be removed during the vaginal portion of the surgery.

- Specific indications for surgical therapy and not XRT include a current pelvic abscess, the presence of a pelvic kidney, or a history of prior XRT for other indications.
- Ovarian transposition can be considered in some patients who wish to preserve their fertility or preserve their ovarian function. Studies have shown 41% to 71% of patients maintained their ovarian function after XRT with ovarian transposition (22). Ovaries can migrate down and contraceptive therapy should still be encouraged if a salpingectomy is not performed.

RADIATION THERAPY

- Total dosing is prescribed to defined anatomical points. Please refer to Chapter 5 for an involved discussion. The point A total dose should be at least 80 to 90 Gy. The point B dose is at least 50 to 60 Gy. WP EBXRT is usually dosed at 45 to 50.4 Gy. Brachytherapy provides a dose with LDR of 40 Gy, or with HDR of 30 Gy. The HDR rates are 0.6 × the LDR rate.
- The duration of treatment with XRT affects outcomes in cervical cancer. As treatment time lengthens, the OS decreases. The goal is completion of treatment within 56 days. There is a 1% per day decrease in survival if treatment goes beyond 56 days (Table 2.3).
- Chemotherapy is usually given concurrently with XRT. It can be given as cisplatin monotherapy dosed weekly at 40 or 50 mg/m^2 with a maximum of 70 mg, or as combination chemotherapy with cisplatin dosed at 40 or 50 mg/m^2 on day 1 and 5-fluorouracil (5-FU) dosed at 1,000 mg/m^2/day as a continuous infusion for 4 days every 3 weeks. For neuroendocrine tumors, etoposide should be added to cisplatin: cisplatin dosed at 25 mg/m^2 IV days 1-3 and etoposide 100 mg/m^2 IV days 1-3 of a 21 day cycle.
- There is a 25% chance of needing adjuvant XRT following radical hysterectomy for intermediate risk factors in patients with stage IB1 disease. For stages IB2

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Table 2.3 Radiation Therapy Outcomes for Cervical Cancer and Treatment Time Delay

Stage	Treatment time, (wk)	10-year pelvic failure, (%)	10-year disease-specific survival (%)
Stage IB	≤7	5	86
	7.1–9	22	78
	>9	36	55
Stage IIA	≤7	14	73
	7.1–9	27	41
	>9	36	43
Stage IIB	≤7	20	72
	7.1–9	28	60
	>9	34	65

and IIA disease, this possibly increases to about 80%. There are data to suggest that 54% of patients with a tumor less than 4 cm will need adjuvant XRT (7). For those with lesions greater than 4 cm in size, approximately 84% will need adjuvant XRT. Adjuvant XRT recommendations were based on pathological data to include: positive LNs, positive parametria, close margins, and less than 3 mm uninvolved stroma.

- The rate of XRT complications increases in dual therapy patients. In GOG 92, there was a 7% incidence of grade 3 to 4 hematologic, GI, or GU complications in patients who had pelvic XRT after radical hysterectomy versus 2% who received no further treatment (NFT) after radical hysterectomy (23). In the Landoni study, there was a 28% complication rate after radical hysterectomy with adjuvant XRT compared to 12% for definitive XRT alone.

ADJUVANT POSTHYSTERECTOMY TREATMENT

Adjuvant therapies are initiated by 6 weeks postoperatively. Risk factors are based on observational data from GOG 49 (24).

- **Intermediate risk factors** GOG 92 (23): XRT is recommended for intermediate risk factor patients. Please refer to Table 2.4 for risk factor combination that would lead to adjuvant therapies.
- **High-risk factors** GOG 109 (25): Combination chemotherapy (every-3-weeks cisplatin and 5-FU, or weekly cisplatin alone) and XRT are indicated for patients following primary surgical treatment with high-risk factors to include: one or more of the following risk factors: LN metastasis, positive (or close, 0.5 cm) margins, or positive parametria.
- A hemoglobin (Hg) goal of at least 9.4 g/dL has been shown to increase the 5 YS by 9% for patients undergoing XRT (26) but the use of red cell stimulants has been associated with a two times higher risk of DVT. Use of transfusion can increase the Hg but this can be associated with immunosuppression, in addition to the TACO or TRALI reactions. In head, neck, and breast cancers,

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Table 2.4 Intermediate Risk Factors for Cervical Cancer Treatment Stratification

LSVI	Stromal invasion	Tumor size
Positive	Deep one-third	Any
Positive	Middle one-third	≥2 cm
Negative	Deep or middle one-third	≥4 cm
Positive	Superficial one-third	≥5 cm

LSVI, Lymphovascular space involvement.

Source: Adapted from Ref. (23). Sedlis A. A randomized trial of pelvic radiation therapy vs. no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1999;73(2):177–183.

the aggressive use of transfusion and growth factors has been associated with a poorer survival. GOG 191 (27) randomized patients to aggressive transfusion or red cell stimulation for patients undergoing concurrent chemotherapy and XRT to maintain Hg at or above 12 g/dL compared to the standard level of 10 g/dL. This study was closed early due to higher DVT/VTE complications.

ADVANCED DISEASE

Treatment options for stage IVB cervical cancer are limited. Chemotherapy alone or chemotherapy with palliative pelvic XRT are the two main options. Chemotherapy can include cisplatin in combination with a taxane, topotecan, gemcitabine, vinorelbine, and/or bevacizumab.

RECURRENT DISEASE

A full metastatic workup should be performed. If local recurrence alone is demonstrated, different surgical options exist. If there is extensive recurrent pelvic disease or distant metastasis, patients are often treated with chemotherapy and/or palliative XRT.

- Most recurrences are diagnosed within the first 2 years: 50% in the first year; 75% in the second year; 95% of recurrences are diagnosed in the first 5 years.
- "Triad of Trouble": signs of recurrence which indicate that a mass has reached the pelvic sidewall are:
  - Sciatica (compression/invasion of the sciatic nerve)
  - Lower extremity edema (compression of pelvic lymphatics)
  - Costovertebral angle (CVA) tenderness (hydronephrosis from compression/invasion of the ureter)
- Management is based on location, prior therapies given, and patient comorbidities.
  - Surgery:
    - Radical hysterectomy: can be considered if the recurrent tumor is less than 2 cm and limited to the cervix. The rate of complications is high, however, with fistula occurring at 50%, and patients having a 5 YS of 62%.

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        - Pelvic exenteration with/without intraoperative radiation therapy (IOXRT): total, anterior, or posterior. The 5 YS with positive pelvic LNs is 15% to 20% and this must be weighed with the morbidity of the procedure. There are certain patient selection factors that are important when considering exenteration: local extension, positive LNs, peritoneal disease, or malignant ascites are adverse factors related to decreased survival. One study found the following three risk factors predicted survival at 18 months: time to recurrence, size, and preoperative pelvic sidewall fixation.
        - Some protocols include consideration of resection of disease at site of failure in noncentral recurrent disease patients with/without IOXRT. This should be followed by systemic or tumor-directed (or both) therapy in most cases.
    - Chemotherapy: cisplatin and paclitaxel showed an improved response rate compared to cisplatin alone (GOG 169). Topotecan and cisplatin also showed an improvement in PFS but not OS over cisplatin alone (GOG 170). The addition of bevacizumab to cisplatin and paclitaxel has shown further improvement in PFS and OS (GOG 240) (28).
    - Radiation:
        - For radiotherapeutic curative-intent retreatment, patients can be broken down into three categories: central disease, limited peripheral disease, and massive peripheral disease. The central and limited peripheral disease patients are good candidates for curative intent, having a 30% to 70% chance for extended survival.
        - Patients who are candidates for salvage reirradiation include those who are medically inoperable, those who refuse surgery, or in whom surgery is not feasible.
        - External beam doses of 39 to 72 Gy, brachytherapy doses of 60 to 89 Gy, or combination XRT doses up to 90 Gy can be used. This yields 57% control for external beam, 67% for brachytherapy, and 44% for combination therapy (29). For recurrence in the para-aortic region, EBXRT can be delivered, but success rates for adenopathy greater than 2 cm are low. Therefore, resection with combination chemotherapy and XRT can be considered (30).
        - Interstitial XRT implants placed via laparotomy guidance have been reported to yield a 71% rate of local control with 36% of patients having no evidence of disease at follow-up.
        - In the palliative setting, Radiation Therapy Oncology Group (RTOG) protocols have given 3.7 Gy twice daily for two consecutive days at 3- to 6-week intervals repeated up to three times.
        - For palliative intent retreatment, the response rates are low and have a short duration. Combined modality retreatment with chemotherapy in addition to XRT can be considered. Platinum compounds, taxanes, and ifosfamide have a response rate of 20% with a median duration of 4 to 6 months.

Fertility sparing approaches: see Chapter 6 for algorithms.

SURVIVAL

- 5 YS by stage and histology:
    - Stage I: squamous 65% to 90%; adenocarcinoma 70% to 75%
    - Stage II: squamous 45% to 80%; adenocarcinoma 30% to 40%

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- Stage III: squamous 60%; adenocarcinoma 20% to 30%
- Stage IV: squamous less than 15%; adenocarcinoma less than 15%

PROGNOSTIC FACTORS FOR SURVIVAL

- Stage I:
  - LVSI (predicts LN metastasis)
  - Size of tumor
  - Depth of invasion (greater than half the thickness of cervix)
  - Tumor volume (>500 mm^3)
  - Presence of LN metastasis (decreases survival by 50%)
- Stages II to IV:
  - Stage
  - LN metastasis (decreases survival by 50%)
  - Tumor volume
  - Age
  - Performance status

FOLLOW-UP

- Every 3 months for the first 2 years
- Every 6 months for years 3 to 5
- Annually thereafter
- The follow-up visit should include:
  - A directed physical and pelvic examination
  - An annual Pap smear without HPV testing is considered adequate surveillance
  - A Pap smear is not performed within the first 3 months following XRT due to XRT-associated changes
  - Consideration can be given to CT scan of the abdomen and pelvis every 6 to 12 months
  - PET scanning can be considered

NOTABLE TRIALS IN CERVICAL CANCER

- GOG 49: was a prospective surgical pathological study of stage I squamous carcinoma of the cervix. 1,120 patients with stage IA2 or IB tumors were evaluated, 940 patients were eligible, 732 squamous cell tumors were investigated, and 645 patients underwent pelvic and para-aortic LND (PP-LND). Four risk factors were found on multivariate analysis as independently associated with a higher risk of pelvic LN metastasis: greater than one-third cervical stromal invasion, LVSI, tumor size greater than 4 cm, and age ≤ 50 years. On univariate analysis, parametrial involvement and grade were also found to be significant (31).
- GOG 71: showed that there is no improvement in survival with the addition of hysterectomy after XRT. This study evaluated 256 patients with exophytic or barrel-shaped tumors, measuring ≥ 4 cm, who were randomized to EBXRT and brachytherapy, or attenuated EBXRT followed by extrafascial hysterectomy. 25% of the patients had tumors greater than 7 cm. There was a 27% versus 14% decrease in the local recurrence rate, but there was no difference in the OS. The 5Y PFS was 53% for the XRT arm versus 62% for the XRT with adjuvant hysterectomy arm ($p = 0.09$). Disease progression occurred in 46% of

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patients in the XRT arm versus 37% for the XRT with adjuvant hysterectomy arm ($p = 0.07$). XRT dosing was 80 Gy to point A in the XRT arm, whereas the adjuvant hysterectomy arm received 75 Gy to point A. The primary criticism of this study was that the adjuvant hysterectomy arm was underdosed. The study was powered for OS, with PFS as a secondary endpoint. For the subgroup with cervical lesions of 4, 5, or 6 cm, there was a borderline significance for PFS and OS in the adjuvant hysterectomy arm. Paradoxically, cervical tumors of 7 cm or greater had a worse survival when treated with adjuvant hysterectomy (32).

- GOG 92: with 12 years of follow-up, researchers looked at 277 patients with at least two of the following intermediate risk factors: greater than one-third stromal invasion, positive lymphovascular space invasion, or large clinical tumor diameter. These were all stage IB patients who underwent radical hysterectomy with LND and who had negative LNs and negative margins. 70% had tumors greater than 3 cm. 137 patients were randomized to adjuvant XRT (50.4 Gy) and 140 patients received no further therapy. Patients with any combination of two or more risk factors who were treated with XRT were found to have a decreased risk of recurrence. The recurrence rate was 15% with XRT versus 28% for those who were observed over 2 years, yielding a 47% decrease in recurrence risk. At 12 years follow-up, essentially the same decrease in recurrence was seen except for those patients with adenocarcinoma who had a significantly different recurrence of 9% versus 44%. There was no significant difference in OS (Table 2.4) (23,33)
- GOG 123: evaluated 369 bulky stage IB (at least 4 cm) patients who were randomized to XRT followed by hysterectomy versus XRT and concurrent chemotherapy followed by hysterectomy. XRT dosing was 45 Gy EBXRT followed by brachytherapy to a total dose of 75 Gy to point A for both groups. An extrafascial hysterectomy was performed 3 to 6 weeks after XRT. Chemotherapy was dosed with cisplatin at 40 mg/m^2 weekly for a maximum of six doses. With a median follow-up of 36 months, the 3 YS was 79% versus 83% with concurrent chemotherapy. The OS was 74% versus 83% with concurrent chemotherapy. The relative risk (RR) of death was 0.54. The recurrence rate was 37% versus 21% for the concurrent chemotherapy arm with a RR of recurrence of 0.51, favoring chemoradiation. Fewer patients in the concurrent chemotherapy arm had residual disease in the uterus (34).
- GOG 85: evaluated 388 patients with stages IIB to IVA disease. Patients were randomized to either XRT with hydroxyurea at 80 mg/kg twice weekly during XRT, or XRT with cisplatin at 50 mg/m^2 and 5-FU at 1,000 mg/m^2 × 96 hr infusion every 28 days. All had negative para-aortic LNDs. The RR of progression or death was 0.79 (95% CI: 0.62–0.99) in the cisplatin/5-FU (CF) group. There was also a decreased incidence of lung metastasis from 9% to 6% when platinum therapy was given. Survival was significantly better for the patients randomized to CF ($p = 0.018$) (35).
- GOG 120: evaluated 526 patients with stages IIB to IVA with negative para-aortic LNs who were randomized to three arms. XRT was administered concurrently with either hydroxyurea alone, hydroxyurea–5-FU–cisplatin, or cisplatin alone. The dose of hydroxyurea was 2 g/m^2 twice weekly when in combination

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and 3 g/m^2 twice weekly when given alone. The dose of cisplatin when used alone was 40 mg/m^2 weekly, and the dose of cisplatin with 5-FU was 50 mg/m^2 days 1 and 29. 5-FU was dosed as a 96-hour infusion of 1,000 mg/m^2. The RR of PFS or death was 0.55 to 0.57 for the cisplatin-containing groups. There was also a lower rate of lung metastasis with a rate of 3% to 4% versus 10% favoring the cisplatin-containing arms. The OS rate was significantly higher in the cisplatin groups than in the hydroxyurea alone group with RR of death of 0.61 and 0.58, respectively (36).

- GOG 109: evaluated 243 patients staged as IA2 or IB. All were status-post radical hysterectomy and had high-risk factors to include: positive nodes (85%) and/or, positive margins (15%), and/or or positive parametria (15%). Patients were randomized to pelvic EBXRT dosed at 49.3 Gy or pelvic EBXRT with concurrent chemotherapy consisting of cisplatin at 70 mg/m^2 and 5-FU of 1,000 mg/m^2/day for 4 days every 3 weeks for four cycles, two cycles of which were given after completion of XRT. The projected 4Y PFS was 80% versus 63% favoring concurrent chemotherapy, yielding a hazard ratio of 2.01 for PFS and 1.96 for OS. The projected OS rate at 4 years was 71% with XRT alone and 81% with chemoradiation. The toxicity was higher (22% vs. 4%) in the concurrent chemotherapy arm. A reappraisal of the data suggested that concurrent chemotherapy was beneficial specifically for cervical lesions ≥2 cm and for patients with two or more positive LNs. The absolute improvement in 5 YS for adjuvant chemoradiation in patients with tumors ≤2 cm was only 5% (77% vs. 82%), while for those with tumors greater than 2 cm it was 19% (58% vs. 77%). Similarly, the absolute 5 YS benefit was less evident among patients with one nodal metastasis (79% vs. 83%) than when at least two nodes were positive (55% vs. 75%). Furthermore, this study also found that there was a significant difference with respect to histologies. Adenocarcinoma subtypes had a better PFS when treated with combination chemotherapy and XRT (25,37).
- GOG 136: evaluated 86 patients with confirmed para-aortic LN metastases clinically staged I to IVA. Radiation doses were WP-XRT 39.6 to 48.6 Gy, point A intracavitary doses of 30 to 40 Gy, and point B doses 60 Gy combined with a parametrial boost. Extended field XRT was dosed at 45 Gy given with concomitant chemotherapy consisting of 5-FU 1,000 mg/m^2/day for 96 hours and cisplatin 50 mg/m^2 weeks 1 and 5. The 3Y OS was 39% and the 3Y PFI was 34%. Extended field RT with concomitant chemotherapy is feasible with a 3Y PFI of 33%. 90% of the patients completed the study (38).
- GOG 165: evaluated clinically staged IIB, IIIB, and IVA cervical cancer patients who were treated with 45 Gy WP-XRT with a parametrial boost of 5.4 to 9 Gy using HDR or LDR. Standard therapy was weekly cisplatin 40 mg/m^2, and experimental therapy was prolonged venous infusion of 5-FU (PVI-FU) at 225 mg/m^2/day for 5 d/wk for six cycles concurrent with XRT. The study was closed prematurely when an analysis indicated that PVI-FU/XRT had a higher treatment failure rate (35% higher) (RR unadjusted, 1.29) and a higher mortality rate (RR unadjusted, 1.37). There was an increase in the failure rate at distant sites in the PVI-FU arm. The 4Y PFS for the cisplatin group was 57% compared to 50% with the PVI-FU group (NS). The 4Y pelvic failure rate was 16% and 14% in the cisplatin and PVI-FU arms. The distant failure

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rate (including abdominal, para-aortic region, bone, liver, and lung) was higher in the PVI-FU group (29% vs. 18%). The PVI-FU group had a higher failure rate for lung metastases (9% vs. 5%) and abdominal failures (11% vs. 3%). Para-aortic failure occurred in only 7% and 5% of patients in the PVI-FU and cisplatin arms, respectively, despite the fact that only 18% of patients were surgically staged in the para-aortic region (39).

- RTOG-79–20: evaluated 337 patients with stages IB, IIA, and IIB disease without clinically or radiologically involved para-aortic LN who were randomized to external beam WP-XRT dosed at 45 Gy or WP-XRT at 45 Gy plus extended field XRT dosed at 45 Gy. Patients who received WP-XRT alone had a 44% 10Y OS compared to a 55% 10Y OS for patients who had pelvic and PA-XRT. Though not statically significant, the difference between the disease specific survival for the pelvic only XRT arm versus the pelvic and PA-XRT arm were 40% and 42%, respectively. 10 year locoregional failure rate was similar (35% for pelvic only and 31% for pelvic and PA). 10 year incidence of grade 4/5 toxicity in the WP-XRT only arm versus the pelvic and PA arm was 4% and 8%, respectively (40).
- RTOG-90–01: evaluated 380 surgically staged patients (IIB–IVA or IB–IIA > 5 cm in size, or those with positive LN) and randomized them to WP and para-aortic XRT with brachytherapy versus WP-XRT and brachytherapy with concurrent cisplatin and 5-FU (75 mg/m^2/day 1 and 1,000 mg/m^2/day on days 2–5, every 21 days for two cycles). The RR was 0.48 for recurrence favoring cisplatin-based chemoradiotherapy. Total dosing was 85 Gy to point A. The patients in the chemotherapy arm had an improved 8Y OS of 67% versus 41%, and a DFS rate of 61% versus 46%. The chemotherapy arm had a decreased locoregional recurrence rate of 18% versus 35% and distant metastasis of 2% versus 35%. The chemotherapy arm had a nonsignificant increase in PA-LN failures at 7% versus 4% (41,42).
- NCIC cervical cancer trial: this is the only trial to show no difference in survival with concurrent chemotherapy and XRT. 253 patients staged IB greater than 5 cm to stage IVA were included. This trial evaluated XRT versus weekly concurrent XRT and cisplatin (40 mg/m^2) for 4 to 6 weeks. Criticisms of this study were that patients had a lower Hg level and longer treatment times. WP-XRT was dosed at 45 Gy with LDR at 35 Gy × 1 or HDR at 8 Gy 3 × versus the same XRT doses with weekly cisplatin at 40 mg/m^2 × 6. The 5 YS was 62% versus 58% NS (43).
- GOG 169: was a randomized phase III clinical trial with 264 eligible patients. It compared single-agent cisplatin at 50 mg/m^2 in patients with stage IVB, persistent, or recurrent cervical cancer to combination cisplatin and paclitaxel dosed at 50 mg/m^2 and 135 mg/m^2 every 21 days. The addition of paclitaxel improved the response rate (36% vs. 19%, $p = 0.002$) and PFS (4.8 months vs. 2.8 months, $p = 0.001$), but did not impact the median OS (9.7 vs. 8.8 months, p = NS) (44).
- GOG 179: randomized patients with stage IVB, persistent, or recurrent cervical cancer to cisplatin 50 mg/m^2 q21d versus doublet therapy with topotecan 0.75 mg/m^2 days1,2,3 and cisplatin 50 mg/m^2 on day1, q21d. The PFS was 2.9 versus 4.6 months, favoring the topotecan–cisplatin combination. The OS was 6.5 versus 9.4 months ($p = 0.017$), favoring the platinum doublet. The response

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rate was 13% for cisplatin alone versus 27% for the combination. Febrile neutropenia occurred more often with the topotecan–cisplatin arm with 17% versus 8% of patients having complications. Grade 3/4 neutropenia occurred in 70% of patients on the topotecan–cisplatin arm. QOL measures were not significantly different between the two arms. The platinum/paclitaxel regimens were less toxic and easier to administer so these regimens are favored instead (45).

- GOG 204: evaluated 513 patients with stage IVB or recurrent cervical cancer. Four platinum doublets were evaluated. The control arm was cisplatin–paclitaxel. The experimental-to-cisplatin-paclitaxel HRs of death were 1.15 (95% CI: 0.79–1.67) for vinorelbine–cisplatin (VC), 1.32 (95% CI: 0.91–1.92) for gemcitabine–cisplatin (GC), and 1.26 (95% CI: 0.86–1.82) for TC. The HRs for PFS were 1.36 (95% CI: 0.97–1.90) for VC, 1.39 (95% CI: 0.99–1.96) for GC, and 1.27 (95% CI: 0.90–1.78) for TC. Response rates (RRs) for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The trends for RR, PFS, and OS (12.9 vs. 10 months) lead to cisplatin/paclitaxel as the standard/preference with less anemia and thrombocytopenia (46).
- Gemcitabine–cisplatin concurrent chemotherapy for locally advanced cervical cancer. 515 patients with stage IIB to IVA disease were randomly assigned to arm A (cisplatin 40 mg/m^2 and gemcitabine 125 mg/m^2 weekly for 6 weeks with concurrent EBXRT dosed to 50.4 Gy in 28 fractions, followed by brachytherapy dosed 30 to 35 Gy and then two additional 21-day cycles of cisplatin, 50 mg/m^2 on day 1, plus gemcitabine, 1,000 mg/m^2 on days 1 and 8) or to arm B (cisplatin at 40 mg/m^2 weekly and concurrent EBXRT followed by brachytherapy). The PFS at 3 years was 74.4% in arm A versus 65% in arm B. The OS (log-rank $p = 0.0224$; hazard ratio [HR], 0.68; 95% CI: 0.49–0.95) and time to progressive disease (log-rank $p = 0.0012$; HR, 0.54; 95% CI: 0.37–0.79) were both better for arm A. Grade 3/4 toxicities were 86.5% in arm A versus 46.3% in arm B. Problems with this study: the primary endpoint was changed mid-study to PFS; the sample size of approximately 500 evaluable patients was based on the original OS primary endpoint of 436 deaths out of 500 patients at an 80% power (47).
- A second study evaluating cisplatin versus cisplatin–gemcitabine was performed in Asia. 74 patients with II–IVA cervical cancer or stage I–II with positive pelvic/para-aortic LN were included. Of these, 37 were randomized to weekly cisplatin at 40 mg/m^2 and 37 were randomized to weekly cisplatin at 40 mg/m^2 with gemcitabine at 125 mg/m^2 for six cycles. The 3Y PFS was 65.1% for cisplatin alone versus 71% for cisplatin-gemcitabine. ($p = 0.71$) favoring. The 3Y OS was 74.1% for cisplatin versus 85.9% for double therapy but crossed over at 5 years ($p = 0.89$) (48).
- GOG 191: studied 109 eligible patients with stage IIB to IVA cervical cancer with an Hg level less than 14 g/dL. Patients were assigned to concurrent weekly cisplatin and XRT with or without recombinant human erythropoietin (40,000 units SQ weekly) to keep the Hg level at standard levels of 10 g/dL versus ≥ 12 g/dL. Venous thromboembolism (VTE) occurred in 4 of 52 patients receiving chemotherapy and XRT compared to 11 of 57 patients treated with chemotherapy and XRT and erythropoietin, not all considered treatment related. No deaths occurred from VTE. The study closed prematurely, with less than 25% of the planned accrual, due to potential concerns for VTE events with erythropoietin (27).

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- GOG 240: a total of 452 evaluable patients with advanced or recurrent cervical cancer were randomly assigned in a 2 × 2 factorial design to cisplatin 50 mg/m^2 and paclitaxel 135 to 175 mg/m^2 or topotecan 0.75 mg/m^2 days 1 to 3, plus paclitaxel 175 mg/m^2 on day 1. Patients were also randomized to bevacizumab 15 mg/kg. Cycles were repeated every 21 days until disease progression or toxicity. The primary endpoint was OS. The topotecan–paclitaxel doublet was not superior to the cisplatin–paclitaxel doublet. The HR for death was 1.20. The addition of bevacizumab to chemotherapy was associated with an increased OS of 3.7 months (17 vs. 13.3 months; HR for death 0.71; 95% CI 0.54–0.95; $p = 0.004$). and higher response rates (48% vs. 36%; $p = 0.008$). The addition of bevacizumab was associated with HTN grade 2 or higher: 25 versus 2%, VTE: 8 versus 1%, and GI fistula grade 3 or higher: 3 versus 0%. As a supplement, a QOL assessment was performed. The FACT-Cx TOI scores for the 309 completed questioners did not differ significantly between patients who received bevacizumab versus those who did not with a $p = 0.27$ (28,49).
- GOG 263/RTOG-1171: adjuvant XRT versus adjuvant chemoradiation in intermediate risk, stage I–IIA cervical cancer after primary radical hysterectomy and pelvic LND: comparator study is GOG 92. The primary objective was the effect of treatment on recurrence-free survival (RFS) with a secondary objective of OS. An estimated 534 patients were randomized to one of two treatment arms after radical hysterectomy and pelvic LND. Arm I: patients underwent pelvic EBXRT or intensity-modulated radiation therapy (IMXRT) 5 days a week for 5.5 weeks. Arm II: patients received cisplatin IV over 1 to 2 hours on day 1 and XRT as in Arm I. Treatment with cisplatin was once every 7 days at 40 mg/m^2 for up to six courses in the absence of disease progression or unacceptable toxicity. Inclusion criteria: pathologically proven primary cervical cancer I to IIA with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma initially treated with a standard radical hysterectomy with pelvic lymphadenectomy and the following pathological characteristics: positive capillary-lymphovascular space involvement and one of the following: deep third penetration; middle third penetration, clinical tumor ≥2 cm; superficial third penetration, clinical tumor ≥5 cm; negative capillary-lymphatic space involvement; middle or deep third penetration, clinical tumor ≥4 cm. Results pending (50).
- GOG 265: ADXS 11–001 Lovaxin C: advaxis consists of a recombinant strain of *Listeria monocytogenes* that secretes HPV 16 E7 protein, which has been attenuated by partial complementation of prfA, the transcriptional factor needed for expression of *Listeria* virulence. ADXS 11–001 (azalimogene filolisbac) uses a multi-copy episomal expression system to secrete a 76kDa fusion protein consisting of the first 417 amino acids of *Listeria* protein Listerolysin O (LLO) followed by the HPV 16 E7 protein. This induces an immune response that promotes a potent antitumor response targeting the E7 protein. The final results of 50 reviewed patients showed a 38% 12 month survival, which is a 52% improvement over the expected survival rate. The mean CR was 18.5 months ranging from 12.2 to 40.6 months. (51).
- JCOG0505: a phase III trial of 253 women with recurrent or metastatic cervical cancer showed that carboplatin/paclitaxel was not inferior to cisplatin/paclitaxel. The OS was 18.3 months for the cisplatin arm versus 17.5 months for the carboplatin doublet (HR = 0.994; 90% CI 0.79–1.25; $p = 0.32$). For patients who had not received cisplatin previously, the OS for the carboplatin doublet

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compared to the cisplatin doublet was 13 versus 23.2 months (HR 1.57; 95% CI 1.06–2.32). Thus, carboplatin may be used in place of cisplatin as an equally effective alternative (52).

- Veliparib for persistent or recurrent cervical cancer: twice-daily oral veliparib (10 mg) was administered during once-daily IV topotecan (0.6 mg/m²) on days 1 to 5 of each treatment cycle every 21 days until disease progression or toxicity. 27 women were enrolled: there were two partial responses (7% [90% CI: 1%–22%]), there were four with disease progression. Patients with low ICH expression (0–1+) of PARP-1 in their primary uterine cervix cancer were more likely to have a longer PFI (HR = 0.25; p = 0.02) and survival (HR = 0.12; p = 0.005) after veliparib–topotecan therapy. Clinical activity of a veliparib–topotecan combination was minimal in persistent or recurrent uterine cervix cancer patients (53).
- GOG 274/RTOG-1174: the OUTBACK Trial: this randomized phase 3 trial evaluated radiosensitizing cisplatin therapy with or without supplemental carboplatin and paclitaxel chemotherapy after definitive XRT in patients with locally advanced cervical cancer. The primary objective was OS with secondary endpoints of PFS, toxicities, and patterns of recurrence. Arm I: patients received cisplatin IV over 60 to 90 minutes on days 1, 8, 15, 22, and 29. Patients also underwent EBXRT once daily, 5 days a week, for 5 weeks. Patients then underwent high-dose rate, pulsed-dose rate, or low-dose rate intracavitary brachytherapy. Arm II: patients received cisplatin and underwent EBXRT and brachytherapy as in Arm I. Beginning 4 weeks later, patients also received adjuvant chemotherapy comprising paclitaxel IV over 3 hours and carboplatin IV over 1 hour on day 1 for four courses in the absence of disease progression or unacceptable toxicity. Eligible patients were diagnosed with FIGO 2009 stage IB1 and node positive, IB2, II, IIIB, or IVA disease suitable for primary treatment with chemoradiation with curative intent. Results pending (54).
- GOG/RTOG-724: a phase III randomized study of concurrent chemotherapy and pelvic XRT with or without adjuvant chemotherapy in high-risk patients with early-stage (1A2, IB, or IIA) cervical carcinoma following radical hysterectomy with high-risk pathologic features including positive pelvic LN, completely resected positive PA-LN, or positive parametria. Results pending.
- GOG 127v: phase II trial of nab-paclitaxel (Abraxane®) in the treatment of recurrent or persistent advanced cervix cancer. Nanoparticle, albumin-bound paclitaxel (nab-paclitaxel) was administered at 125 mg/m² IV over 30 minutes on days 1, 8, and 15 of each 28-day cycle to 37 women with metastatic or recurrent cervix cancer that had progressed or relapsed following first-line cytotoxic drug treatment. 35 eligible patients were enrolled, all patients had one prior chemotherapy regimen and 27 had prior XRT with concomitant cisplatin. The median number of nab-paclitaxel cycles was four (range 1–15). Ten (28.6%; CI 14.6%–46.3%) of the 35 patients had a PR and 15 patients (42.9%) had SD. The median PFS and OS were 5.0 and 9.4 months, respectively. The only NCI CTCAE grade 4 event was neutropenia in two patients (5.7%). Grade 3 neurotoxicity was reported in one (2.9%) patient. Nab-paclitaxel has considerable activity and moderate toxicity in the treatment of drug-resistant, metastatic, and recurrent cervix cancer (55).
- GOG 263: 534 patients with stage I–IIA cervical cancer were reviewed. All had ≥2 intermediate risk adverse pathologic factors (Sedlis criteria from GOG 92)

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after radical hysterectomy and pelvic LND. Patients were randomized to WP-XRT vs cisplatin at 40 mg/m^2 weekly and WP-XRT; Outcomes pending (56).

- Senticol 1: 133 patients with FIGO stage IA–IB1 cervical cancer were evaluated between 2005 and 2007 in this prospective feasibility study. All underwent laparoscopic radical hysterectomy and SLN identification. If the frozen section on the SLN was negative they were randomized to completion full pelvic and para-aortic LND or no further dissection. SLN identification was via combined technetium and patent blue injections. Histology included squamous, adeno, and adenosquamous carcinoma. 14% of patients had nodal micrometastasis. 9% of patients had adjuvant chemoradiation due to adverse prognostic factors. Five year results include: 8% recurred, 5% died of disease progression, there was no difference in PFS or OS, there were no false negatives (57).
- Senticol 2: 206 were patients randomized to radical hysterectomy with SLND with or without completion LND: 105 patients were in the SLN alone group and 101 were in the complete pelvic LND group. No false negatives were identified in the complete LND arm. 3 year follow up reviewed surgical morbidity and showed a 51.5% rate of morbidity compared to a 31.4% rate with SLND alone (morbidities not specified) (58).
- Laparoscopic Approach to Cervical Cancer (LACC) trial: a randomized phase II trial comparing outcomes in radical hysterectomy patients via laparotomy versus laparoscopy. Results pending (59).
- SHAPE Trial: a randomized trial comparing radical hysterectomy and pelvic node dissection versus simple hysterectomy and pelvic LND in patients with low-risk early stage cervical cancer. To demonstrate that simple hysterectomy and LND is not inferior to radical hysterectomy and LND in terms of pelvic relapse rate and is associated with better quality of life/sexual health. Results pending.
- INTERLACE Trial: INduction ChemoThERapy in Locally Advanced CErvical Cancer. A randomized controlled trial of carboplatin AUC 2 and paclitaxel 80 mg/m^2 weeks 1–6 followed by standard cisplatin-based chemotherapy at 40 mg/m^2 weekly with XRT weeks 7 to 13, versus standard cisplatin-based chemotherapy with XRT. Results pending.
- TAKO trial: a randomized controlled trial of weekly cisplatin at 40 mg/m^2 versus every 3 week cisplatin at 75 mg/m^2 in combination with XRT in locally advanced stage IIB to IVA cervical cancer. Results pending.
- TACO trial: is a randomized controlled trial of tri-weekly cisplatin at 75 mg/m^2 for 3 cycles with concurrent XRT in locally advanced cervical cancer compared to weekly cisplatin at 40 mg/m^2 for 6 cycles with XRT in patients staged IB2, IIB-IVA. Results pending.

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Tubo-Ovarian Cancers: Ovarian, Fallopian Tube, and Primary Peritoneal

CHARACTERISTICS

- Upon review of pathogenesis for high-grade serous adnexal cancers and reflecting standard clinical practice, ovarian, fallopian tube, and primary peritoneal cancers have now been classified uniformly as high-grade serous tubo-ovarian cancers (HGSTOC). Sex cord stromal and germ cell tumors (GCT) are classified separately and considered to originate from the ovary itself. The more uncommon epithelial subtype origin is undetermined. One in 70 women will develop tubo-ovarian cancer in their lifetime. In 2017, 22,440 new cases are approximated with 14,080 deaths. As awareness has increased regarding the possible origin of HGSTOC, close histolopathologic review can identify the transition within the fallopian tubes from benign to serous carcinoma (Figure 2.3).

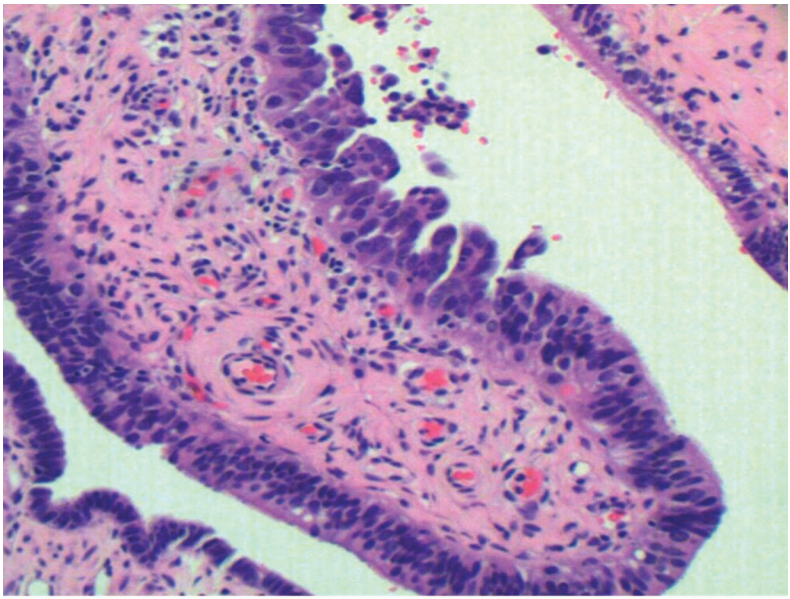

Figure 2.3 Serous tubal intraepithelial carcinoma (STIC) identified in a patient surgically staged as 3C HGSTOC.

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- Serous tubo-ovarian cancer (STOC) is most commonly found in advanced stage: 84% of women present with stage IIIC and 12% to 21% present with stage IV disease. Most women die from bowel complications/obstruction.
  - Symptoms include abdominal fullness, dyspepsia, constipation, tenesmus, pelvic fullness or pressure, bloating, and anorexia. Many of these make up the ovarian cancer symptom index.
  - The route of spread for tubo-ovarian cancer is primarily transcoelomic. Cancer cells flake off the ovarian/fallopian tube surface and implant throughout the abdomen and pelvis. Other routes of spread are lymphatic and hematogenous.

PRE-TREATMENT WORKUP

- The pre-treatment workup includes a history and physical examination, lymph node (LN) survey, and laboratory tests, including a CBC, CMP, coagulation profile, CA-125, and other indicated tumor markers. A CXR is recommended in addition to abdominal/pelvic imaging (CT/MRI). Colonoscopy and esophagoduodenoscopy can be considered based on symptoms. Specific attention should be given to pain elicited during the pelvic exam, the presence of a mass that is fixed or solid, the presence of nodularity, and the overall mobility of the rectosigmoid colon and parametrium (Figures 2.4 and 2.5).

Figure 2.4 Ovarian cancer/pelvic mass CT.

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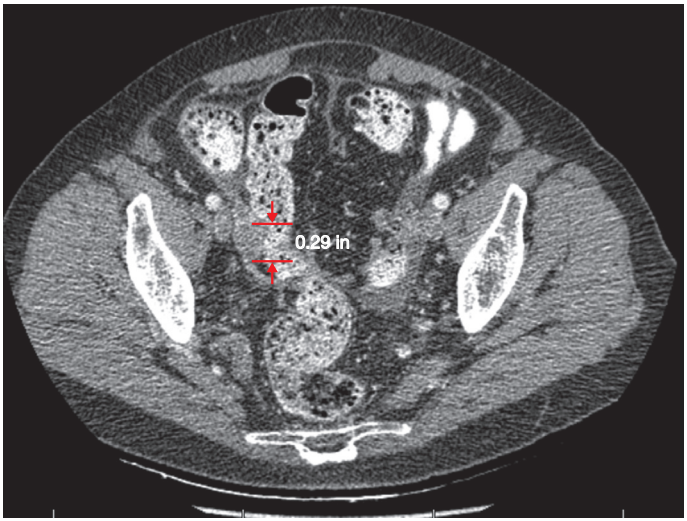

Figure 2.5 Partial large bowel obstruction from high-grade serous tubo-ovarian cancer (HGSTOC).

TREATMENT

- Primary treatment can be surgical (PDS-primary surgical debulking) or with neoadjuvant chemotherapy (NACT).
- Surgery usually consists of an exploratory laparotomy, abdominal cytology, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and cytoreduction.
- Patients with evidence of up to stage IIIB cancer should be surgically staged to include peritoneal biopsies and a pelvic and para-aortic lymph node dissection (LND). Three-fourths of advanced-stage cancers will have positive retroperitoneal LN. LN drainage tends to follow the ovarian vessels. Dissection around the high precaval and para-aortic regions is important.
- The definition of complete debulking is removal of all gross tumor to no residual visible disease (microscopic status): R0. Optimal debulking is removal of all gross tumor to less than 1 cm visible macroscopic disease: R1. Suboptimal resection is defined as remaining visible tumor with a diameter greater than 1 cm: R2.
- Surgical staging is often inadequate when performed by general surgeons (68%) or general gynecologists (48%), compared to gynecologic oncologists (3%).
- If neoadjuvant chemotherapy is chosen as primary treatment, surgical debulking should follow after 2–3 cycles of chemotherapy.

HISTOLOGY

- World Health Organization (WHO) classification of tubo-ovarian tumors:
  - Common epithelial
    - Serous: high grade and low grade
    - Mucinous
    - Seromucinous
    - Endometrioid

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- Clear cell
- Brenner
- Mixed epithelial
- Undifferentiated
- Mixed mesodermal
- Unclassified

- Sex cord stromal ovarian tumors
  - Granulosa stromal cell
    - Granulosa cell
    - Thecoma–fibroma
  - Androblastoma: Sertoli–Leydig cell tumors
    - Well-differentiated Pick's adenoma (Sertoli cell tumor)
    - Intermediate differentiation
    - Poorly differentiated
    - Heterologous elements
  - Lipid cell tumors
  - Gynandroblastoma
  - Unclassified
- Germ cell ovarian tumors
  - Dysgerminoma
  - Endodermal sinus tumor
  - Embryonal carcinoma
  - Polyembryoma
  - Choriocarcinoma
  - Teratoma
    - Immature
    - Mature: dermoid cyst
    - Monodermal: carcinoid, struma ovarii
  - Mixed
  - Gonadoblastoma
- Soft tissue tumors
- Unclassified
- Metastatic secondary tumors: 5% to 6% of adnexal masses are metastases from the breast, gastrointestinal tract, or urinary tract.

STAGING

FIGO staging was last amended in 2014. Staging is surgical (Table 2.5)

Table 2.5A AJCC 8th Edition: T Category

T	FIGO	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	IA	Tumor limited to one ovary (capsule intact) or fallopian tube surface; no malignant cells in ascites or peritoneal washings

(*continued*)

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Table 2.5A AJCC 8th Edition: T Category (*continued*)

T	FIGO	T criteria
T1b	IB	Tumor limited to one or both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following
T1c1	IC1	Surgical spill
T1c2	IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	IC3	Malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below the pelvic brim, or primary peritoneal cancer
T2a	IIA	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	IIB	Extension to and/or implants on other pelvic tissues
T3	III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis, and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) LNs
T3a	IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement, with or without positive retroperitoneal LNs
T3b	IIIB	Macroscopic peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension, with or without metastasis to the retroperitoneal LNs
T3c	IIIC	Macroscopic peritoneal metastasis beyond the pelvis, more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal LNs (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

LN, lymph nodes.

Table 2.5B AJCC 8th Edition: N Category

N	FIGO	N criteria
NX		Regional LNs cannot be assessed
N0		No regional LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) not greater than 0.2 mm
N1	IIIA1	Positive retroperitoneal LN only (histologically confirmed)
N1a	IIIA1i	Metastasis up to 10 mm in greatest dimension
N1b	IIIA1ii	Metastasis more than 10 mm in greatest dimension

LN, lymph nodes.

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Table 2.5C AJCC 8th Edition: M Category

M	FIGO	M criteria
M0		No distant metastasis
M1	IV	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal LNs and LNs outside the abdominal cavity); and transmural involvement of intestine
M1a	IVA	Pleural effusion with positive cytology
M1b	IVB	Liver or splenic parenchymal metastases: metastases to extra-abdominal organs (including inguinal LNs and LNs outside the abdominal cavity); transmural involvement of intestine

LN, lymph nodes.

Table 2.5D AJCC 8th Edition: Stage Grouping

When T is	And N is	And M is	Then the stage group is:
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T1c	N0	M0	IC
T2	N0	M0	II
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1/T2	N1	M0	IIIA1
T3a	N0/N1	M0	IIIA2
T3b	N0/N1	M0	IIB
T3c	N0/N1	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

EPITHELIAL TUBO-OVARIAN CANCER

CHARACTERISTICS

- Risk factors for epithelial ovarian cancer (EOC) include age (median age of 61 years), low or nulliparity, infertility, and genetic risk.
- Genetic mutations: the *BRCA 1* and *2* genes are located on chromosome 17q21 and 13q12-13, respectively. Mutations in these genes can cause autosomal

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dominant inherited forms of familial cancer and yield a combined 80% overall risk of tubo-ovarian cancer; 11% to 25% of patients of serous TOCs harbor one of these mutations: Rad50/51C/51D, BRIP1, BARD1, CHEK2, MRE11A, MSH2, MLH1, MSH6, PMS2, PPM1Df, POLE, POL-D1, PALB2, 17SNPs, NBN, PALB2, TP53. Hereditary nonpolyposis colon cancer (HNPCC) yields a 10% risk of tubo-ovarian cancer and can present with other cancers such as endometrial cancer (60% risk), colon cancer (60% risk), and urothelial cancers.

- The use of oral contraceptive pills and pregnancy reduce the overall risk (relative risk [RR] = 0.66). OCPs also reduce risk for HGSTOC in carriers of genetic mutations.
- 10% to 14% of apparent early-stage ovarian cancers are staged IIIA1i/ii (based exclusively on retroperitoneal LN involvement).
- The ovaries can be "fertile soil" for metastatic disease. Metastatic disease can be distinguished from a primary ovarian tumor by the following: metastatic tumors to the ovaries are bilateral in 77% of cases, have multifocal and nodular implants, and often smaller in size. Primary tumors are commonly larger than 17 cm and usually unilateral (bilateral only in 13%).
- Terminology has been suggested to distinguish between low-grade and high-grade tubo-ovarian cancers. It is not universally adopted.
  - Type I tumors are the low-grade serous tumors. This is distinct from low malignant potential (LMP)/borderline tumors.
    - The annual incidence is 3.8%, with an overall survival (OS) of 99 months. Diagnosis is with low mitotic activity (below 12 mitosis/per 10 HPF [high power field]). 99% are found at stage III. Even with six cycles of chemotherapy, 88% of patients had stable disease (a 5% ORR). Nine percent respond to hormonal treatment. Bevacizumab has been shown to provide a sustained complete response (CR) in recurrent disease (1).
    - Type I tumors respond to chemotherapy, although not as vigorously as type II because chemoresistance is due to the low growth fraction. In an in vitro chemoresponse profile: 86% of tumors demonstrated a sensitive chemoresponse assay result to at least one agent, 35.7% were pan-sensitive to all seven standard cytotoxic agents: carboplatin, cisplatin, docetaxel, doxorubicin, gemcitabine, paclitaxel, topotecan (2). 23% of low grade (LG) STOC responded in an arbeitsgemeinschaft gynaekologische onkologie (AGO) database (3).
  - Type II tumors are the most common type of tubo-ovarian-type cancers, namely high-grade serous. 80% to 90% of HGSTOC respond to standard chemotherapies (Figure 2.6A and B).

PRE-TREATMENT WORKUP

Workup follows the general preoperative/staging workup as described earlier.

HISTOLOGY (Table 2.6)

- Serous carcinoma is the most common type of EOC. Serous cancers are graded in a two-tiered fashion: low grade and high grade. **Immunohistochemistry Profiling for STOC**: p53+, WT-1 positive, PAX-8 positive, ER/PR indeterminate, CK7+ (see Figures 2.6A and B)

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- Clear cell carcinoma: these tumors are difficult to treat; 63% are refractory to primary platinum chemotherapy. There is an increased risk of deep vein thrombosis (DVT): 42% versus 18% when compared to serous histologies in one study (4). There is a 15% rate of venous thromboembolism (VTE) during primary treatment, and 9% occurrence at the time of recurrence in another study (5). The OS is approximately 12 months for patients with advanced-stage disease.
- Mucinous carcinoma tumors are often large and serum CEA can be positive. They have a higher rate of discordance between frozen and final pathology at 34%: 11% were downgraded and 23% were upgraded. This is due in part to their larger size. LN metastases are rare in apparent stage I cancers and an LND can potentially be omitted in these cases without adverse effect on progression-free survival (PFS) or OS (6). Appendectomy is still recommended to ensure primary tumor site identification.
- Brenner tumors: Brenner tumors of the ovary are relatively uncommon neoplasms, constituting 1.4% to 2.5% of all ovarian tumors. Histologically a Brenner tumor is characterized by varying numbers of rounded nests of transitional or squamous-like epithelium and glandular structures of cylindrical cells within

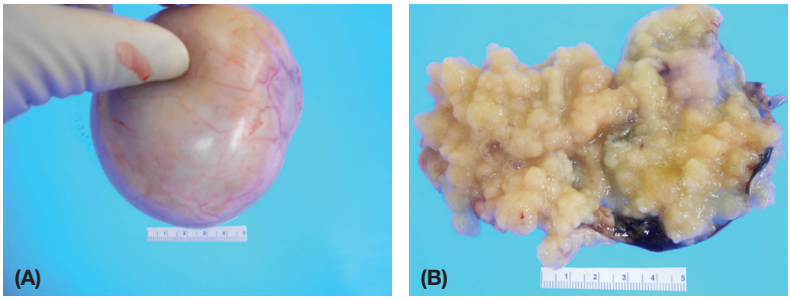

Figure 2.6 (A) Exterior of pelvic mass. (B) Gross bivalve of same pelvic demonstrating papillary projections of HGSTOC.

Table 2.6 Epithelial Ovarian Cancer Histological Subtypes

Histologic subtypes	Percent of malignant epithelial ovarian tumors	Percent bilaterality
Serous	46	73
Mucinous	36	47
Endometrioid	8	33
Clear cell	3	13
Transitional	2	
Mixed	3	
Undifferentiated	2	
Unclassified	1	
Brenner	1.5	

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abundant fibrous nonepithelial tissue. Most Brenner tumors are benign, only 2% to 5% being malignant. Malignant components of the tumor show heterogeneous epithelial growth and atypia with intervening stroma, consist of transitional cells, squamous or undifferentiated carcinoma, or a mixture of these types. The criteria proposed by Hull and Campbell in 1973 are as follows (a): frankly malignant histologic features must be present (b), there must be intimate association between the malignant element and a benign Brenner tumor (c), mucinous cystadenomas should preferably be absent or must be well separated from both the benign and the malignant Brenner tumor (d), and stromal invasion by epithelial elements of the malignant Brenner tumor must be demonstrated.

STAGING

Follows FIGO and AJCC surgical staging protocols.

- Upstaging based on LN metastasis has been reviewed in 14 studies. The mean incidence of LN metastases in clinical stages I to II EOC was 14.2% (range 6.1%–29.6%) of which 7.1% were only in the para-aortic region, 2.9% only in the pelvic region, and 4.3% in both the para-aortic and pelvic regions (7). Grade 1 tumors had a mean incidence of LN metastases of 4.0%, grade 2 tumors 16.8%, and grade 3 tumors 20.0%. According to histologic subtype, the highest incidence of LN metastases was found in the serous subtype (23.3%), the lowest in the mucinous subtype (2.6%). Patterns of LN metastases were largely independent of laterality: among those with unilateral lesions and positive nodes, 50% had ipsilateral LN involvement, 40% had bilateral involvement, and 7% to 13% had isolated contralateral positive LN (8).

TREATMENT

Treatment is usually primary surgical staging with debulking if indicated, followed by adjuvant chemotherapy for all tumors staged greater than IA grade 1. Neoadjuvant chemotherapy followed by surgery can be considered for patients who are poor surgical candidates (large pleural effusions with poor ventilation capacity, severe congestive heart failure (CHF), recent myocardial infarction (MI), recent pulmonary embolus) or who have extensive disease that is potentially unresectable (based on operative skill, patient comorbidities, or risk scoring). Optimal debulking to no visible residual disease is the primary goal. Adjuvant chemotherapy treatment should start within 25 days of surgery. Each additional 10% cytoreduction of disease yields a 5.5% increase in median survival (9).

- Cytoreductive surgery for stage IV TOC can be attempted with 30% achieving optimal cytoreduction; 30% of patients can be expected to have complications (mostly infectious or wound). The preoperative performance status should be two or lower. Bristow et al (10) demonstrated that survival depended on location of the stage IV disease: the median survival for patients with a pleural effusion was 19 months, lung metastasis was 12 months, parenchymal liver metastasis was 18 months, and other extraperitoneal sites were 26 months. If patients had liver metastasis and had optimal intra- and extrahepatic cytoreduction to less than 1 cm, the median OS was 50 months; if there was optimal extrahepatic and suboptimal hepatic resection, the median OS was 27 months; and if there was suboptimal resection at all sites, there was an OS of 8 months.

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- Removal of LNs for advanced-stage disease has been studied (11); 427 patients with stage IIB, IIIC, or IV all underwent optimal surgery, including removal of bulky LNs greater than 1 cm in diameter. Intraoperative randomization was performed and the control arm completed optimal surgery, whereas the treatment arm underwent additional retroperitoneal lymphadenectomy to remove pelvic (at least 25 nodes) and para-aortic (at least 15 nodes) LNs. After surgery, all patients received platinum-based chemotherapy. The 5Y progression free interval (PFI) was 31.2% for the LND group compared to 21.6% for those in the control arm. The LND group was more likely to require blood transfusions, had a longer surgery, and had more postoperative complications. At 68.4 months, 202 of the 427 patients had died. There was no difference in the risk of death: 48.5% of the LND group and 47% of the control group were alive 68.4 months after surgery.
- Predictive models for optimal surgical cytoreduction
  - Different presurgical models have attempted to stratify predictive values of various findings for optimal debulking versus candidacy for neoadjuvant therapy (ascites, carcinomatosis, tumor size, CA-125 level) but the proposed models usually fail with validation sets. False-positive criteria range from 10% to 68% for laboratory, clinical, or radiologic criteria. If there is progressive disease (refractory disease) while on NACT, a change in chemotherapy regimen should be considered. If the tumor has regressed, it is appropriate to surgically assess the patient and attempt surgical debulking.
  - A surgical assessment algorithm has been proposed with the potential to categorize patients by location and bulk of disease into theoretically optimally resectable versus not resectable, called: "scope and score" based on the Fagotti score. Care should be taken with this approach as surgeons are passionate about their surgical skill but can vary differently in their opinions and skill sets (12).
    - Fagotti score (seven parameters). Laparoscopic evaluation for feasibility of primary debulking surgery (PDS) versus unresectable to optimal disease status. If patients are deemed not optimally resectable, they are thus dispositioned to neoadjuvant chemotherapy (NACT). It was externally validated and modified by Brun (13) (Table 2.7)

Table 2.7 Scoring System for HGSTOC

Laparoscopic feature	Score 0	Score 2
Peritoneal carcinomatosis	Carcinomatosis involving a limited area (along the paracolic gutter or the pelvic peritoneum) and surgically removable by peritonectomy	Unresectable massive peritoneal involvement as well as with a military pattern of distribution
Diaphragmatic disease	No infiltrating carcinomatosis and nodules confluent with the most part of the diaphragmatic surface	Widespread infiltrating carcinomatosis or nodules confluent with the most part of the diaphragmatic surface

(*continued*)

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Table 2.7 Scoring System for HGSTOC (*continued*)

Laparoscopic feature	Score 0	Score 2
Mesenteric disease	No large infiltrating nodules and no involvement of the root of the mesentery as would be indicated by limited movement of the various intestinal segments	Large infiltrating nodules or involvement of the root of the mesentery indicated by limited movement of the various intestinal segments
Omental disease	No tumor diffusion observed along the omentum up to the large stomach curvature	Tumor diffusion observed along the omentum up to the large stomach curvature
Bowel infiltration	No bowel resection was assumed and no military carcinomatosis on the ansae observed	Bowel resection assumed or military carcinomatosis on the ansae observed
Stomach infiltration	No obvious neoplastic involvement of the gastric wall	Obvious neoplastic involvement of the gastric wall
Liver metastasis	No surface lesions	Any surface lesion

HGSTOC, high grade serous tubo-ovarian cancers.

- If tubo-ovarian cancer is diagnosed incidentally after a TH-BSO without staging, surgical staging should be considered within 3 weeks. The risk of undiagnosed higher-stage disease is 22% to 29% (14); 4% to 25% of unstaged clinical stage I ovarian cancers have positive LNs, and the incidence of isolated contralateral positive LNs ranges from 7% to 13%.
- The timing of ovarian cyst rupture can make a difference. According to one study (15), preoperative cyst rupture had a larger influence on PFS than intraoperative cyst rupture. For preoperative cyst rupture, the hazard ratio (HR) for OS was 2.65 versus 1.64 for intraoperative cyst rupture (16).
- Tumor biology: the impact of disease distribution in stage III ovarian cancer patients was evaluated (17): 417 patients from three randomized Gynecologic Oncology Group (GOG) trials who were microscopically cytoreduced and given adjuvant IV platinum/paclitaxel were reviewed. Patients were divided into three groups based on preoperative disease burden: minimal disease (MD) was defined by pelvic tumor and retroperitoneal metastasis; abdominal peritoneal disease (APD) was considered disease limited to the pelvis, retroperitoneum, lower abdomen, and omentum; and upper abdominal disease (UAD) was considered disease affecting the diaphragm, spleen, liver, or pancreas. The median OS was not reached in MD patients, 80 months in the APD group, and 56 months in the UAD group ($p < 0.05$). The 5Y survival (YS) was 67% for MD group, 63% for APD and 45% for UAD. In multivariate analysis, the UAD group had a significantly worse prognosis than MD and APD both individually and combined (PFS HR 1.44; $p = 0.008$ and OS HR 1.77; $p = 0.0004$). Thus, it is

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suggested that there is a biological difference in ovarian cancer patients proportional to the amount of disease at presentation.

CHEMOTHERAPY FOR EPITHELIAL TUBO-OVARIAN CANCER

- **First-line chemotherapy** involves platinum-based chemotherapy regimens with a taxane. Single-agent platinum regimens can be considered in older or compromised patients.
- **Second-line agents** are used when cancer recurs after first-line therapy has been given.
  - **Platinum-sensitive and platinum-resistant disease**. This is defined based on disease recurrence in relation to the 6 month time period following completion of first-line platinum-based chemotherapy.
    - Platinum sensitive disease: tumor has recurred but more than 6 months has elapsed since primary treatment with platinum-containing regimens. Second line chemotherapy with platinum-based regimens should be used.
    - Platinum resistance is defined as: disease recurrence occurring less than 6 months after completion of primary platinum-based treatment. If recurrence occurs at less than 6 months, non–platinum-based salvage therapies should be used.
    - Platinum refractory is defined as: patients who have progressive disease while on chemotherapy.
    - Response rates for second-line chemotherapy depend on the time to recurrence after primary chemotherapy. The longer the interval from primary therapy, the better the response rate: 6 to 12 months, 27%; 13 to 24 months, 33%; greater than 24 months, 59%
- **Neoadjuvant chemotherapy** is chemotherapy given prior to surgery. Surgery is usually attempted after two to three cycles of chemotherapy. This has been shown to reduce the radical nature of surgery with a decreased risk of colostomy and hemorrhage.
- **Consolidation:** chemotherapy that is used after primary or adjuvant chemotherapy to decrease the chance of cancer recurrence in patients with complete clinical remission (CCR). This is usually a short duration of treatment.
- **Maintenance:** chemotherapy that is used after primary or adjuvant chemotherapy to decrease the chance of cancer recurrence in patients with CCR. This is usually of a longer duration than consolidation therapy.
- **Intraperitoneal (IP) chemotherapy:** chemotherapy is administered directly into the abdominal cavity. IP chemotherapy using platinum and taxane regimens is indicated for optimally debulked patients stage II or higher.
- **Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC):** heated cytotoxic regimens are administered at the time of primary or recurrent debulking surgery and circulated intraperitoneally for a specific amount of time.
  - Benefits:
    - A high volume of chemotherapy can be delivered, and a homogeneous distribution can be achieved. This is often not practical in conventional IP therapy, because of abdominal distension and pain, but it is feasible in HIPEC, since the patient is under anesthesia.

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    - There is no interval between cytoreduction and chemotherapy. The cytotoxic therapy is applied at the time of minimal disease manifestation, and there are no adhesions that might alter the distribution of the drug.
    - Hyperthermia (>41°C) has a pharmacokinetic benefit. Several studies have convincingly shown that hyperthermia can increase both the tumor penetration of cisplatin as well as DNA crosslinking.
    - High concentrations of chemotherapy can be achieved in the IP compartment with low systemic exposure—in a single intraoperative treatment.
    - There is the mechanical continuous flow of perfusion solution.
  - Many combinations of cytotoxic agents have been used:
    - Single agents to include: carboplatin 800 mg/m^2 for 60 to 120 minutes at 41°C to 43°C; oxaliplatin 460 mg/m^2 for 30 minutes; cisplatin 100 mg/m^2 for 90 minutes at 41°C to 43°C.
    - Cisplatin 350 mg/m^2 and alpha-interferon 5 million IU/m^2 and for 90 minutes at 43°C to 44°C; cisplatin 100 mg/m^2 and mitomycin C 15 mg/m^2 for 60 minutes at 41°C to 43°C; paclitaxel 60 to 75 mg/m^2 and cisplatin 100 mg/m^2 or doxorubicin 0.1 mg/kg (if platinum resistant) for 120 minutes at 40°C to 43°C.
  - However, the absence of sufficient levels of scientific evidence to support the use of HIPEC in patients with tubo-ovarian cancer with peritoneal dissemination does not allow a general recommendation outside of clinical trials.

TREATMENT BY STAGE

- Stage IA grade 1 tumors: surgery is definitive. If fertility preservation is a concern, consider leaving the uterus and contralateral tube and ovary.
- Stage IA, grade 2 or 3 and stage IB and IC, any grade: primary treatment is surgery. If fertility is a concern, consider leaving the uterus and contralateral tube and ovary. Adjuvant chemotherapy is platinum based with a taxane for three to six cycles.
- Stages II, III, IV: either NACT or PDS may be offered. NACT has been shown to offer lower peri- and postoperative morbidity but PDS may offer superior survival (18).
  - Primary treatment is surgery (PDS). Adjuvant chemotherapy is platinum based with a taxane for six cycles. This can be administered IV or IP/IV.
  - Consideration can be given to neoadjuvant chemotherapy for:
    - The medically unfit or high perioperative risk patient.
    - Per surgical risk assessment score (Fagotti).

SECOND-LOOK LAPAROTOMY

- Second-look laparotomy is the pathological surgical assessment for residual disease after primary adjuvant chemotherapy in a patient with a clinical complete response. It is used to guide decisions for either continuing chemotherapy, changing chemotherapy, or discontinuing chemotherapy. It can also be used to guide treatment in patients who were suboptimally debulked, or who were primarily unstaged. Routine second-look laparotomy is not the current standard of care; 40% of second-look patients are pathologically positive, and of those who are negative, 50% will recur (see Table 2.8) (19).

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Table 2.8 Second-Look Laparotomy for HGSTOC 5 YS Outcomes

Second-look laparotomy disease status	5Y survival (%)
No evidence of disease	50
Microscopic	35
Macroscopic	5

RECURRENCE

- Most recurrences occur within the first 2 years. The risk of recurrence for a grade 1, stage I ovarian cancer is less than 10%. The risk of recurrence for stage III ovarian cancer is much higher, over 50%.

SECONDARY CYTOREDUCTION

- Secondary cytoreduction is the removal of gross recurrent disease after primary or secondary chemotherapy. There are some criteria attributed to Chi, which help stratify patients as appropriate surgical candidates. These are based on time, location, and number of recurrent tumor sites. If the recurrence occurs at greater than 30 months from primary chemotherapy, secondary cytoreduction can be attempted regardless of number of involved sites. If the interval is less than 30 months, and there are one to two sites of recurrence, cytoreduction can again be attempted. If there is carcinomatosis, ascites, or the patient is platinum resistant, it is often not wise to attempt secondary cytoreduction. For those who had less than 0.5 cm of residual disease after secondary cytoreduction, an improvement in OS to 56 months was seen versus 27 months for those who were suboptimally debulked. The overall success at secondary optimal cytoreduction ranges between 24% and 84% (20).

CEREBELLAR DEGENERATION

- Cerebellar degeneration can occur from antibodies to ovarian cancer. This is called **paraneoplastic cerebellar degeneration.** The incidence is 2:1,000 patients with gynecologic cancers. There are two main antibodies: the anti-Yo antibody reacts against the Purkinje cells and the anti-Hu antibody reacts against all neurons.

SURVIVAL

- Relative survival
- 2 YS: 65%; 5 YS: 44%; 10 YS: 36% (21) (Tables 2.9 and 2.10)
- 10 YS: 31% of women survive more than 10 years. Younger age, early stage, low grade, and nonserous histology are significant predictors of long-term survival. One third of those who survived to 10 years had stages III or IV per 1989 staging, 16% of patients with late-stage serous cancer survived more than 10 years (22).

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Table 2.9 HGSTOC 5Y Survival by Stage	
Stage	**Relative 5Y survival (%)**
I	90
IA	94
IB	92
IC	85
II	70
IIA	78
IIB	73
III	39
IIIA	59
IIIB	52
IIIC	39
IV	17
HGSTOC, high grade serous tubo-ovarian cancer.	

Table 2.10 5Y Survival by Residual Disease	
Residual disease	5 YS
Microscopic	40%–75%
Optimal	30%–40%
Suboptimal	5%
YS, year survival.	

SURVIVAL CARE

- Follow-up:
  - Every 3 months for 2 years
  - Every 6 months up to 5 years
  - Annually for subsequent visits
- At each visit:
  - Physical and pelvic examination
  - Symptom review
  - Consider CA-125: discussion should be held with the patient regarding surveillance with tumor markers. Rustin et al demonstrated no improvement in survival when tumor markers were followed. Patients had a poorer quality of life with additional unsuccessful cycles of chemotherapy given based on laboratory data. Assessment of symptoms, along with physical examination, can guide the clinician regarding when to order lab tests, imaging, and when to initiate second-line chemotherapy (23).
- CT imaging: CT cannot often detect subcentimeter disease.

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EPITHELIAL TUBO-OVARIAN CANCER NOTABLE TRIALS

- **Primary Adjuvant Chemotherapy Trials**
  - ICON 1: this trial evaluated 477 patients who had early ovarian cancer "staged" with hysterectomy, bilateral salpingo-oophorectomy, and recommended omentectomy. Eligibility was if the treating physician was uncertain whether the patient required chemotherapy. 93% of patients were "stage I." Patients were randomized between no further treatment (NFT) and single-agent carboplatin (AUC 5); cisplatin, doxorubicin, cyclophosphamide (CAP); or another platinum regimen. Histology was: 32% serous, 15% clear cell, 23% mucinous. Most patients were apparent stage I; however, there were 7% of patients with stage II or III disease; 70% were grade 2 or 3. At 51 months, the OS was 79% in the chemotherapy arm versus 70% in the NFT arm. The 5Y PFS was 73% in the chemotherapy group versus 62% in the NFT group. For clinical stage I disease that did not get staged, there was a 38% recurrence rate without further treatment and a 30% death rate. Chemotherapy had an HR of 0.66 for survival (24).
  - ACTION: this trial ran concurrently with ICON 1. 30% of 448 patients were comprehensively staged. Patients were randomized to observation or to chemotherapy. Chemotherapy consisted of four to six cycles of single-agent platinum or a platinum-containing regimen. 40% of patients were stage IA or IB and 60% had grade 1 or grade 2 disease. The 5 YS in the observation and adjuvant chemotherapy arms were 75% and 85%. Patients who received chemotherapy had a better recurrence-free survival (RFS; HR 0.63). In nonoptimally staged patients, the adjuvant chemotherapy group had an improved OS and RFS (HR 1.75 and HR 1.78, respectively). Among patients in the observation arm, optimal staging provided an improvement in OS and RFS (HR 2.31 and HR 1.82, respectively). There was no benefit seen from adjuvant chemotherapy in the optimally staged patients. This suggests that in the suboptimally staged group, there were undiagnosed higher-staged patients who benefited when given chemotherapy. A 10Y follow-up found support for most of the original conclusions, except that OS after optimal surgical staging was improved, now among patients who received adjuvant chemotherapy (HR of death 1.89) (25,26).
  - ICON 2: this trial evaluated 1,526 eligible surgically staged patients who needed primary adjuvant chemotherapy. Patients were staged I to IV and were randomized to single-agent platinum-based chemotherapy or CAP. This trial was stopped early due to the availability of taxanes. These patients were then grouped into the control arm of ICON 3 as their outcomes were statistically nonsignificant with an OS HR of 1.0. The median survival in both groups was 33 months and the 2 YS was 60% for both arms. CAP was more toxic (27).
  - ICON 3: this trial evaluated 274 eligible surgically staged patients stages I to IV, 20% of whom were stages I and II. Patients were randomized between a paclitaxel–carboplatin doublet versus the ICON 2 group of single-agent carboplatin or CAP. The OS was 36 months for carboplatin–paclitaxel and 35 months for the control groups of single-agent carboplatin and CAP. The PFS were 17 months versus 16 months for the control arm. There were a lot of confounding factors in this study: a large number of patients were deemed

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to have recurrent disease based on elevated CA-125 levels prior to showing clinical recurrence. In addition, 30% of those who did not get paclitaxel as primary treatment received paclitaxel as second-line treatment (28).

- ICON 4: this trial evaluated 802 eligible patients with recurrent platinum-sensitive ovarian cancer; 75% recurred more than 12 months following initial therapy. Patients were randomized to paclitaxel 175 to 185 mg/m^2 and cisplatin 50 mg/m^2 or carboplatin AUC 5 versus single-agent cisplatin 75 mg/m^2 or carboplatin AUC 5. The doublet therapy showed a statistically significant improvement over the single-agent group with a median PFS of 13 months versus 10 months (HR 0.76; $p = 0.0004$). The doublet therapy showed an improvement in median survival by 5 months (29 months versus 24 months; HR of 0.82, $p = 0.02$). This translated to a 2 YS of 57% versus 50% and a 1Y PFS of 50% versus 40%. Criticisms of this trial were that 75% of patients were in a good prognosis group. This is essentially a trial of platinum-sensitive disease (28).
- ICON 5/GOG 182 EORTC 55012: this trial evaluated 4,312 surgically staged stage III and IV patients for primary adjuvant therapy. The control arm was the doublet of carboplatin AUC 6 and paclitaxel 175 mg/m^2 administered for eight cycles. The experimental arms consisted of carboplatin–paclitaxel–gemcitabine as sequential doublets or in triplicate, for a total of eight cycles, or carboplatin–paclitaxel–topotecan as sequential doublets for a total of eight cycles, and carboplatin–paclitaxel–liposomal doxorubicin as a triplicate regimen for eight cycles. There was no difference in median PFS or OS with the PFS in the control arm being 16 months and the OS being 44 months, both in the optimally and suboptimally debulked patients. The median PFS for patients with suboptimal, gross optimal (<1 cm residual), and microscopic residual disease were 13, 16, and 29 months, respectively, and the median OS rates were 33, 40, and 68 months, respectively (29).
- ICON 7/AGO-OVAR 11: this trial evaluated 1,528 eligible patients stages I to IV, of whom 26% were suboptimally debulked. The control arm was carboplatin AUC 5 or 6 and paclitaxel 175 mg/m^2 IV every 3 weeks for six cycles. The experimental arm consisted of carboplatin and paclitaxel at the same doses with the addition of bevacizumab at 7.5 mg/kg IV every 3 weeks for six cycles, with maintenance bevacizumab continued for an additional 12 cycles or until progression of disease. Median follow-up was 48.9 months. At 42 months, PFS was 22.4 months without bevacizumab versus 24.1 months with bevacizumab ($p = 0.04$ log rank). In high-risk patients, the PFS was 14.5 months versus 18.1 months with bevacizumab and median OS was 28.8 versus 36.6 months with bevacizumab. At 48.9 months though, no difference in PFS was seen. For the entire population at 48.9 months, the restricted mean survival time (RMST; OS) demonstrated an improvement of only 0.9 months from 44.6 to 45.5 months (95% confidence interval [CI] log rank $p = 0.85$, pH test $p = 0.02$) with bevacizumab—not significant (NS). In a subgroup analysis, RMST for the poor prognosis group (stage IV, inoperable stage III [6%], and suboptimally debulked >1 cm stage III) demonstrated a 4.8-month RMST improvement from 34.5 to 39.3 months (log rank $p = 0.03$ PH test = 0.007). In the average prognosis group, the RMST was 49.7 months versus 48.4 months

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(p = 0.2) in the bevacizumab group. No benefit from bevacizumab was seen in low-grade serous tumors, clear cell tumors, or low-stage high-risk patients (stage I–IIA clear cell or G3). Hypertension attributed to bevacizumab was seen in 18% of patients who received bevacizumab versus 2% of patients in the control arm. Bowel perforation was seen in 10 patients in the bevacizumab group versus three patients in the control arm (30,31).

- GOG 1: 86 evaluable surgical stage I patients were randomized to observation, whole pelvic radiation therapy (WP-XRT), or melphalan chemotherapy. Recurrence was 17% in the observation group, 30% in those irradiated, and 6% in those who received chemotherapy. Recurrence was related to grade: grade 1, 11%; grade 2, 22%; grade 3, 27% (32).
- GOG 111: this trial evaluated 386 eligible suboptimally debulked stage III and IV patients. Patients with greater than 1 cm residual disease were randomly assigned to receive cisplatin 75 mg/m^2 and cyclophosphamide 750 mg/m^2 or cisplatin 75 mg/m^2 and 24-hour paclitaxel 135 mg/m^2. Overall response rate in the first arm was 73% compared to 60%. PFS was longer in the paclitaxel-containing arm at 17.9 months versus 12.9 months. OS was longer in the paclitaxel arm at 37.5 months compared to 24.4 months (33).
- OV-10: this trial evaluated cyclophosphamide and cisplatin versus 3-hour paclitaxel and cisplatin in 680 eligible patients with stage IIB, IIC, III, or IV disease, who were optimally and suboptimally debulked. The ORR was 58.6% in the cisplatin and paclitaxel arm versus 44.7% in the cyclophosphamide and cisplatin arm. The PFS was 15.5 months versus 11.5 months favoring the paclitaxel arm and the OS was 35.6 months versus 25.8 months, again, all favoring paclitaxel (34).
- GOG 132: this trial evaluated 648 suboptimal stage III and any stage IV patients. There were three arms: a doublet of cisplatin and paclitaxel dosed at 75 and 135 mg/kg; single-agent paclitaxel dosed at 200 mg/kg; and single-agent cisplatin dosed at 100 mg/kg. The PFS, respectively, were 14 months, 11 months, and 16 months. The OS, respectively, were 26 months, 26 months, and 30 months. The response rates were, respectively, 67%, 67%, and 47% (35).
- GOG 157: this trial evaluated three versus six cycles of paclitaxel and carboplatin in 427 eligible patients staged IAG3, IBG3, IC, and II. The primary endpoint was recurrence rate. 457 patients were registered, 213 in each arm. Of these, 70% were stage I, 30% were stage II, and there were 30% clear cell cancers in each arm. The recurrence rate was 27.4% for three cycles versus 19% for six cycles (95% CI: 0.53–1.13). The probability of surviving 5 years was 81% for three cycles versus 83% for six cycles (95% CI: 0.66–1.57). The HR for recurrence was 0.74, p = 0.18 (NS). Criticisms of the study were: insufficient power to detect a difference, and only 29% (126) of patients were staged appropriately. Chan updated the data in 2006 and found a benefit to six cycles of chemotherapy specifically for serous tumors with a 5Y RFS of 83% compared to 60% in those who received six versus three cycles of chemotherapy, respectively (p = 0.007). Those with serous tumors had a significantly lower risk of recurrence after six versus three cycles of chemotherapy (HR 0.33; 95% CI: 0.14–0.77; p = 0.04) in contrast to nonserous tumors (HR 0.94; 95% CI: 0.60–1.49) (36,37).

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- GOG 158: this trial compared 792 optimally cytoreduced stage III ovarian cancer patients to 24-hour paclitaxel and cisplatin versus 3-hour paclitaxel and carboplatin. This was designed as a noninferiority study and there was provision for second-look laparotomy, which about 50% chose to do (Greer et al subset analysis proved that second-look laparotomy was not beneficial). 85% were able to receive all six cycles. The PFS was 19 months for paclitaxel and cisplatin and 20 months for paclitaxel and carboplatin. The OS was 48 months for paclitaxel cisplatin and 57 months for paclitaxel carboplatin. The RR of recurrence was 0.88 (95% CI: 0.75–1.03), and the RR for the OS was 0.84 (95% CI: 0.7–1.02) favoring carboplatin and paclitaxel. The carboplatin arm had less myelotoxicity and electrolyte problems, with similar neurotoxicity (19,38).
- GOG 218: this randomized trial evaluated 1,873 staged III or IV suboptimally debulked patients with a control arm of carboplatin and paclitaxel. The investigational arms consisted of carboplatin and paclitaxel with either bevacizumab for 5 months during primary therapy or an extended dosing of bevacizumab after six initial cycles of carboplatin, paclitaxel, and bevacizumab for a total of 18 cycles. The PFS was, respectively, 10.3, 11.2, and 14.1 months; the PFS HR was 0.91/0.72. The OS, respectively, was 39.9, 38.7, and 39.7 months; OS HR was 1.036/0.92. Maximum separation of the PFS occurred at 15 months and the curves merged 9 months later. The degree of neutropenia was associated with a greater PFS and OS (HR 0.76 and 0.73, respectively) (39).
- SCOTROC 1: this trial evaluated 1,077 patients with stage IC to IV disease and randomized them to docetaxel 75 mg/m^2 versus paclitaxel at 175 mg/m^2 each with carboplatin at an AUC of 5 for six cycles. The PFS was 15 months versus 14.8 months. Docetaxel was found to not be inferior. The OS was 64.2% versus 68.9%, respectively (40).
- OCTAVIA: this single-arm study evaluated 189 patients treated with primary adjuvant bevacizumab plus weekly paclitaxel and every 21 days carboplatin. For patients with stage IIB to IV or grade 3/clear-cell stage I/IIA, bevacizumab was dosed at 7.5 mg/kg on day 1; paclitaxel at 80 mg/m^2 on days 1, 8, 15; and carboplatin at an AUC 6 on day 1 IV every 21 days for six to eight cycles, followed by single-agent maintenance bevacizumab to total 1 year. 74% of the patients had stage IIIC/IV disease. The primary objective was PFS. Patients received a median of six chemotherapy and 17 bevacizumab cycles. At the predefined cutoff 24 months after last patient enrollment, 99 patients (52%) had progressed and 19 (10%) had died, all from ovarian cancer. The median PFS was 23.7 months (95% CI: 19.8–26.4 months), 1Y PFS rate was 85.6%, response evaluation criteria in solid tumors (RECIST) response rate was 84.6%, and median response duration was 14.7 months. Most patients (≥90%) completed at least six chemotherapy cycles. Grade ≥3 peripheral sensory neuropathy occurred in 5% and febrile neutropenia in 0.5%. There was one case of gastrointestinal perforation (0.5%) and no treatment-related deaths (41).
- AGO-OVAR 9: This was a randomized phase III front-line chemotherapy trial by the Gynecologic Cancer InterGroup (GCIG) for previously untreated patients with stages I to IV epithelial ovarian cancer. 1,742 patients were randomly allocated to receive a combination of paclitaxel, carboplatin, and gemcitabine (TCG) or paclitaxel and carboplatin (TC). TC was given day 1 every

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21 days for a planned minimum of six courses. Gemcitabine was given on days 1 and 8 of each cycle in the TCG arm. The median PFS for the TCG arm vs TC arm was 17.8 months and 19.3 months, respectively (HR 1.18; 95% CI: 1.06–1.32; $p = 0.0044$). The median OS for TCG and TC arm was 49.5 months and 51.5 months, respectively. Patients on the TCG arm experienced more grade 3 to 4 hematologic toxicity and fatigue compared to patients treated on the TC arm. Quality of life analysis showed a disadvantage in the TCG arm (42).

- AGO-OVAR 10/MIMOSA study: abagovomab is an anti-idiotypic antibody produced by mouse hybridoma and generated against OCA-125. Abagovomab maintenance therapy or placebo was administered as a 2 mg 1 mL suspension once every 2 weeks for 6 weeks then once every 4 weeks until recurrence for up to 21 months after primary surgery with adjuvant platinum–taxane chemotherapy in 888 EOC patients randomized in a 2:1 ratio. A robust immune response was seen but the HR for RFS and OS were 1.099 (95% CI: 0.919–1.315; $p = 0.301$) and 1.15 (95% CI: 0.872–1.518; $p = 0.322$), respectively. A prior phase I/II trial of 119 patients showed prolonged survival in those who demonstrated an immune response to vaccination (23.5 vs. 4.9 months) contrary to this phase III trial (43).
- AGO-OVCAR 12/LUME-Ovar1: (Nintedanib) 1,366 women with stage IIB to IV with EOC underwent PDS to R1/R0 status. Patients were randomly assigned (2:1) to receive six cycles of carboplatin (AUC 5 mg/mL/min or 6 mg/mL/min) and paclitaxel (175 mg/m^2) in addition to either 200 mg of nintedanib (nintedanib group) or placebo (placebo group) twice daily on days 2 to 21 of every 3-week cycle for up to 120 weeks. The primary endpoint was PFS. Addition of antiangiogenic to standard chemotherapy increased median PFS in the nintedanib group versus the placebo group (17.2 months [95% CI: 16.6–19.9] vs. 16·6 months [95% CI: 13.9–19.1]; HR 0.84 [95% CI: 0.72–0.98]; $p = 0{\cdot}024$). The most common adverse events (AEs) were: diarrhea in the nintedanib group at 22% versus in the placebo group at 3%: and neutropenia in the nintedanib group (42%) versus placebo (36%). Serious AEs were reported in 42% of the nintedanib group and 34% of the placebo group; 2% of patients in the nintedanib group experienced serious AEs associated with death compared with 3% in the placebo group. Nintedanib in combination with carboplatin and paclitaxel prolonged the PFS in first-line treatment of ovarian cancer patients with a higher impact in patients with low postoperative tumor burden (44).
- AGO-OVAR 15: this was randomized phase II study that compared carboplatin, paclitaxel and lonafarnib to carboplatin and paclitaxel alone as frontline treatment in 105 EOC patients FIGO stages IIB to IV. Lonafarnib was dosed at 100 mg PO BID during chemotherapy and increased to 200 mg for up to 6 months after chemotherapy for maintenance therapy. PFS was 11.5 months in the lonafarnib, carboplatin and paclitaxel taxol (LTC) arm versus 16.4 months in the TC arm ($p = 0.0141$) and the median OS was 20.6 months versus 43.4 months in the TC arm ($p = 0.012$). For those with R1–R2 disease, lonafarnib was inferior treatment, thus, further investigation was not recommended (45).
- AGO-OVAR-17 (**B**evacizumab **O**varian **O**ptimal **S**tandard **T**reatment [BOOST]) Trial: a prospective randomized phase III trial to evaluate

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optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube, or peritoneal cancer. 927 patients with FIGO stages IIB to IV EOC were randomized 1:1 to paclitaxel 175 mg/m^2 and carboplatin AUC 5 q21 days with bevacizumab 15 mg/kg q21 days with an additional 22 cycles of bevacizumab: versus paclitaxel 175 mg/m^2 and carboplatin AUC 5 q21 days with bevacizumab 15 mg/kg q21 days with maintenance bevacizumab for an additional 44 cycles. NCT01462890: results pending.

- GOG 241: carboplatinum/paclitaxel ± bevacizumab versus oxaloplatin–capacetabine ± bevacizumab as first-line therapy in advanced or recurrent chemonaive mucinous EOC. NCT01081262: results pending.

- **Dose Density Trials**
  - GOG 97: this study investigated four cycles versus eight cycles of cyclophosphamide and cisplatin in 458 eligible patients. The four-cycle regimen dosed the chemotherapy doublets at 1,000/100 mg/m^2 whereas the eight-cycle doublet dosed the chemotherapy at 500/50 mg/m^2 given every 3 weeks. This provided no difference in OS, and the total dosing was the same (46).
  - Fruscio weekly cisplatin: this trial evaluated 285 eligible patients and randomized them to weekly cisplatin at 50 mg/m^2 for 9 weeks versus cisplatin at 75 mg/m^2 for six cycles every 3 weeks. At 16.8 years follow-up, no difference in PFS was seen (17.2 months vs. 18.1 months, HR 1.08) and no difference in OS was seen (35 months vs. 32 months, HR 0.97) for the dose dense weekly cisplatin versus standard treatment (47).
  - The Scottish Dose Dense Trial: this trial evaluated six cycles of cyclophosphamide at 750 mg/m^2 and cisplatin at doses of either 50 or 100 mg/m^2 q21 days in 159 patients. The OS for the 100 and 50 mg/m^2 patients was 32.4% and 26.6%, and the overall relative death rate was 0.68 ($p = 0.043$). From this trial, the standard 75 mg/m^2 dose was chosen for its modest toxicity (48).
  - The Dutch/Danish Study: this trial randomized 222 patients between different doublet doses of carboplatin and cyclophosphamide. Carboplatin was dosed at an AUC of either 4 or 8 q28 days for six cycles in combination with cyclophosphamide at a constant dose of 500 mg/m^2. There was no difference in OS (2 YS 45%) or complete pathologic response (32% and 30%) (49).
  - Gore et al. randomized 227 patients to single-agent carboplatin at either an AUC of 6 for six courses or an AUC of 12 for four courses every 4 weeks. There was no difference in PFS or OS at 5 years at 31% and 34%, respectively. There was more toxicity in the AUC 12 arm (50).
  - GOG 134: this trial included 271 eligible patients with persistent, recurrent, or progressive disease who were evaluated with paclitaxel dosed at 135 mg/m^2/24 hr, paclitaxel at 175 mg/m^2/24 hr, or paclitaxel at 250 mg/m^2/24 hr. The 135 mg/m^2 arm was closed early. The partial and complete response to paclitaxel at 250 mg/m^2 (36%) was higher than those receiving 175 mg/m^2 (27%, $p = 0.027$). The median duration for OS was 13.1 months and 12.3 months for paclitaxel 175 and 250 mg/m^2, respectively. Thus, paclitaxel exhibited a dose effect with regard to response rate, but there was no survival benefit (51).
  - European–Canadian randomized trial of paclitaxel in relapsed ovarian cancer: this trial evaluated infusion length of paclitaxel in recurrent ovarian

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cancer in 391 eligible patients. This was a 2 × 2 study design of 3-hour versus 24-hour infusion and 135 mg/m^2 versus 175 mg/m^2. The high-dose group had a longer PFS at 19 weeks versus 14 weeks ($p = 0.02$). The 175 mg/m^2 dose was found to have a better response rate at 19% versus the 135 mg/m^2 dose with a response rate of 16% (NS). There was no difference in survival (52).

- NOVEL Trial: New Ovarian Elaborate Trial JGOG 3016: this phase III trial evaluated 631 patients with stages II, III, and IV EOC patients, stratified by residual disease less than 1 cm or greater than 1 cm as well as by histology (clear cell/mucinous vs. serous/others) to carboplatin AUC 6 q21 days for six to nine cycles versus dose dense weekly paclitaxel 80 mg/m^2 on days 1, 8, 15 with carboplatin AUC 6 day 1 q21 days for six to nine cycles. Carboplatin was dosed at an AUC 6 and given every 3 weeks with either: weekly paclitaxel at 80 mg/m^2 or standard 3-week dosing at 180 mg/m^2. The median follow-up was 76.8 months. The median PFS was 28.2 months (95% CI: 22.3–33.8) versus 17.5 months ([15.7–21.7]; HR 0.76; 95% CI: 0.62–0.91; $p = 0.0037$). The median OS was 100.5 months (95% CI: 65.2–∞) in the dose-dense treatment group and 62.2 months (95% CI: 52.1–82.6) in the conventional treatment group (HR 0.79; 95% CI: 0.63–0.99; $p = 0.039$). The HR for progression was 0.71 (95% CI: 0.58–0.88; $p = 0.0015$). The 3Y OS was 72% versus 65% ($p = 0.03$), respectively. The 5Y OS was 58.6% versus 51.0%, respectively, with an HR of 0.79 (53,54).
- GOG 262: 692 patients were enrolled in a phase III randomized trial in which 84% elected to receive bevacizumab in addition to either paclitaxel 175 mg/m^2 every 3 weeks with carboplatin AUC 6 for six cycles, or paclitaxel dosed weekly 80 mg/m^2 plus carboplatin AUC 6 for six cycles. In the intention-to-treat analysis, weekly paclitaxel was not associated with longer PFS than paclitaxel administered every 3 weeks (14.7 months and 14.0 months, respectively; HR for progression or death = 0.89; 95% CI: 0.74–1.06; $p = 0.18$). For those patients who did not receive bevacizumab, weekly paclitaxel was associated with PFS that was 3.9 months longer than that observed with paclitaxel administered every 3 weeks (14.2 vs. 10.3 months; HR 0.62; 95% CI: 0.40–0.95; $p = 0.03$ This is similar to JGOG 3016 outcomes). However, among patients who received bevacizumab, weekly paclitaxel did not significantly prolong PFS, as compared with paclitaxel administered every 3 weeks (14.9 months and 14.7 months, respectively; HR 0.99; 95% CI: 0.83–1.20; $p = 0.60$). A test for interaction that assessed homogeneity of the treatment effect showed a significant difference between treatment with bevacizumab and without bevacizumab ($p = 0.047$). Patients who received weekly paclitaxel had a higher rate of grade 3 or 4 anemia than did those who received paclitaxel every 3 weeks (36% vs. 16%), as well as a higher grade 2 to 4 sensory neuropathy (26% vs. 18%); although lower rates of grade 3 or 4 neutropenia (72% vs. 83%) were observed. Weekly paclitaxel, compared to every 21 day paclitaxel did not prolong PFS (55).
- MITO7 (dose intense): 810 patients with stages IC to IV EOC were randomized in a 1:1 fashion to carboplatin AUC 6 and Taxol 175 mg/m^2 every 3 weeks for six cycles versus carboplatin AUC 2 and paclitaxel 60 mg/m^2 every week for 18 weeks. Primary endpoints were PFS and quality of

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life (QOL). The median follow-up was 22.3 months. The median PFS was 17.3 months for every 3 week treatment versus 18.3 months for weekly treatment; HR 0.96; 95% CI: 0.8–1.16; $p = 0.66$. The weekly group had less neutropenia and neuropathy. 25% had neoadjuvant chemotherapy, 24% were not operated on, 23% were suboptimally debulked, 25% were stage IV, and 67% were serous histology. The 2 YS was 79% with every 3-week treatment and 77% with weekly treatment. This was not a dose-dense study so is not a parallel to the JGOG study (56).

- ICON 8: an international phase III randomized trial of dose fractionated chemotherapy compared to standard three weekly chemotherapy, following immediate primary surgery or as part of delayed primary surgery, for women with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer. Arm 1 (Control arm): carboplatin and paclitaxel on day 1 of a 21-day cycle for six cycles: carboplatin administered IV at AUC 5 and paclitaxel 175 mg/m^2 IV. Arm 2: carboplatin AUC 5 on day 1 and dose-fractionated weekly paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 21-day cycle for six cycles. Arm 3: dose-fractionated weekly carboplatin AUC 2 and weekly paclitaxel 80 mg/m^2 on day 1, 8, and 15 of a 21-day cycle for six cycles. Results pending.

- **IP Trials**
  - GOG 104: this trial evaluated 546 patients for primary adjuvant chemotherapy after "optimal" debulking to a size of less than 2 cm. IV cyclophosphamide was given at 600 mg/m^2 for six cycles every 3 weeks with either IP cisplatin or IV cisplatin (both dosed at 100 mg/m^2). The median OS was significant favoring the IP arm at 49 months versus the IV group at 41 months. The HR for death was lower in the IP group, 0.76; 95% CI: 0.61 to 0.96; $p = 0.02$ (57).
  - GOG 114: this trial evaluated 462 stage III patients who were optimally debulked to less than 1 cm. Patients were randomized to IV cisplatin at 75 mg/m^2 and IV paclitaxel 135 mg/m^2 over 24h every 3 weeks for six cycles versus IV carboplatin at an AUC 9 for two cycles q28 days followed by IP cisplatin at 100 mg/m^2 with IV paclitaxel 135 mg/m^2 over 24h every 3 weeks for six cycles. Second-look laparotomy was optional. The PFS was 27.6 months versus 22.5 months with $p = 0.01$, the OS was 63.2 months versus 52.5 months with a $p = 0.05$, all favoring IP therapy (58).
  - GOG 172: this trial evaluated 415 stage III patients who were optimally debulked to less than 1 cm residual. Patients were randomized to either IV paclitaxel at 135 mg/m^2 over 24 hours, with cisplatin dosed at 75 mg/m^2 or to IP cisplatin on day 1 dosed at 100 mg/m^2 with IV paclitaxel at 135 mg/m^2 over 24 hours on day 2, and paclitaxel again on day 8 dosed at 60 mg/m^2 IP. 64% had gross residual disease after primary surgery and 50% of patients chose a second-look surgery. 41% of the IV group versus 57% of the IP group had a pathologic complete response at second-look laparotomy (SLL). Only 42% of the IP group completed all IP cycles whereas 83% of the IV group received all six cycles. The PFS was 18.3 months for the IV arm versus 23.8 months for the IP arm ($p = 0.05$). The OS was 49.7 months for the IV arm versus 65.6 months

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for the IP arm with a 16-month survival advantage favoring IP therapy (p = 0.03). A 5.5-month PFS was seen. Patients with no visible residual disease did well with a 78-month median survival for those on the IV arm and the median survival has not been reached for the IP arm (59).

- A 10Y follow-up of GOG 114 and 172: a combined review of two IP studies including 876 patients showed the median PFS for IP therapy was 25 months compared to 20 months for IV therapy. The OS was 61.8 versus 51.4 months, respectively. The risk of death decreased by 12% for each cycle of IP chemotherapy completed. The disease-free survival (DFS) for those who received IP therapy with R0 disease (complete cytoreduction) was 60.4 months, with an OS of 127.6 months (60).
- Prognostic factors for stage III EOC treated with IP chemotherapy: a combined review of surgically debulked patients on GOG IP studies 114 and 172: a second 10Y follow-up of GOGs 114 and 172. IP versus IV OS was 61.8 months versus 51.4 months with risk reduction of death 23%. Those patients with R0 disease who received IP therapy had a PFS of 38 months with a median OS not yet reached and a median follow-up of 53 months. An OS of 127 months with R0 disease after PDS was seen in this subgroup. The OS for those treated on the IV arm with R0 disease was 78 months. The difference in the median OS between the IV and IP arms was 16 months, the difference between RD1 versus RD0 exceeded 39 months. Considering all patients in GOGs 114 and 172: the difference in OS between the IV and IP arms was 11 months, while the difference between RD1 and RD0 for those receiving IP was over 60 months. This then concludes there is huge value in resecting all gross disease with acceptable morbidity. 29% of patients underwent bowel resection, which is a surrogate for surgical effort (61).
- 205 patients randomized to IP therapy on GOG 172: of these, 58% did not complete treatment, 13% did not receive IP treatment, 57% completed one to two cycles, 29% received three to five cycles. 34% were not able to complete treatment because of catheter-related issues, 38% due to poor tolerance to the treatment, 29% did not have IP treatment because of disease progression of other complications (62).
- GOG 9921: this was a phase I feasibility study evaluating dose modification of GOG 172. 23 patients were evaluated. IP cisplatin was dosed at 75 mg/m^2 with IV paclitaxel at 135 mg/m^2 over 3 hours on day 1, with IP paclitaxel 60 mg/m^2 administered on day 8, of a 21-day cycle with a 95% rate of adherence for an outpatient regimen (63).
- **IP catheter outcomes** GOG 172: of the 58% of patients not completing six IP cycles, one third were catheter-related (catheter infection in 20 of 41 cases, blocked catheter in 10 of 41 cases). One third were related to IP treatment (pain, bowel complications, patient refusal, other noncatheter infection). One third of discontinuations were probably unrelated to the catheter (nausea, renal, metabolic). Left colon resection or colostomy related to a decreased ability to tolerate IP chemotherapy. Appendectomy, small bowel resection, or right colon surgery did not appear to affect IP tolerance. Optimal placement is the use of a 9.6-F catheter through a separate incision (not the laparotomy incision), and tunneled at least 10 cm, with 10 cm length

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left in the peritoneal cavity. A waiting time of 24 hours post-insertion before use was recommended to avoid leakage (64).

- GOG 252: this was a phase III trial of patients with stage II to IV epithelial tubo-ovarian cancer to include suboptimally debulked patients. 1,560 patients were randomized to one of three arms: Arm 1 (control arm similar to GOG 262): IV paclitaxel at 80 mg/m^2 weekly with IV carboplatin AUC 6 every 3 weeks and IV bevacizumab 15 mg/kg every 3 weeks continuing with maintenance bevacizumab × 22 weeks. Arm 2: IV paclitaxel 80 mg/m^2 weekly with IP carboplatin AUC 6 every 3 weeks and IV bevacizumab 15 mg/kg every 3 weeks with maintenance bevacizumab × 22 weeks. Arm 3: IV paclitaxel at 135 mg/m^2 on day 1 followed by IP cisplatin at 75 mg/m^2 on day 2, then IP paclitaxel at 60 mg/m^2 on day 8 and bevacizumab at 15 mg/kg every 3 weeks with maintenance bevacizumab for 22 weeks. The median age was 58, 34% were stage III, 10% stage II, 72% were G3 serous, 57% achieved R0 debulking, 90% in Arm 1 completed platinum therapy, 90% in Arm 2, and 84% in Arm 3. PFS was the primary outcome. Median PFS for the 461 patients in Arm 1 was 26.8 months, for the 464 patients in Arm 2 was 28.7 months (log rank $p = 0.661$), and for the 456 patients in Arm 3, was 27.8 months (log rank $p = 0.122$). Of note: this was not a platinum dose intense trial similar to GOG 172, and bevicuzimab was added as primary therapy and maintenance, similar to GOG 218 (64).
- iPocc Trial (GOTIC-001/JGOG-3019): the target accrual is 746. In this trial, dose-dense weekly paclitaxel at 80 mg/m^2 was administered in combination with carboplatin AUC 6 every 3 weeks either IV or IP. Eligible patients had EOC stages II to IV. This study will explore the potential of IP chemotherapy to include suboptimally debulked advanced ovarian cancer (65).
- OV-21/GCIG study led by the Canadian National Cancer Institute: all patients with stage III EOC will receive neoadjuvant chemotherapy. Those patients who respond to the neoadjuvant chemotherapy will receive interval debulking surgery (IDS), and if the residual disease after IDS becomes the optimal (less than 1 cm), the patient will be randomized to one of the three arms. The control arm is the combination of IV paclitaxel at 135 mg/m^2 followed by IV carboplatin at AUC 5 on day 1, and then IV paclitaxel at 60 mg/m^2 will be given on day 8. The second arm is same as the control arm but carboplatin will be given by the IP route. The third arm is the modified GOG 172 winner arm, which is the same as the third arm of GOG 252 trial but in which bevacizumab is not given. One of these two IP arms (Arm 2 or Arm 3) will be chosen, in a randomized phase II manner, and the winner arm will be compared with the control arm as a phase III trial. Results pending.

- **Maintenance/Consolidation Trials**
  - GOG 178: this trial evaluated consolidation therapy in 222 eligible stage III and IV patients and randomized patients to 12 versus 3 cycles of paclitaxel at 175 mg/m^2 after completion of six cycles of platinum/paclitaxel with a clinical complete response. At 50% enrollment, the protocol dictated interim analysis. This showed an improvement in PFS favoring 12 cycles with an HR of 2.31 demonstrating a 28 month versus 21 month PFS ($p = 0.002$ 99% CI: 1.08 to 4.94). The study was closed at this point. Patients were allowed to crossover so all those on the three-cycle arm could complete up to 12 cycles of therapy (66).

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- Follow-up study to GOG 178: criticisms cited from this study were the crossover may have masked a difference between study arms, there was insufficient power within the study, and treatment at relapse equalized outcomes. The PFS was 22 versus 14 months favoring the 12-month paclitaxel. OS was 53 versus 48 months ($p = 0.34$ NS) (67).
- Initiation of salvage chemotherapy; a retrospective institutional evaluation of maintenance therapy vs. expectant management in patients with recurrent disesase reviewed 59 eligible patients with a median follow-up of 51 months. The median time from CCR to start of second-line chemotherapy was 21 months; the median time to the start of third-line agents was 43 months. 12 months elapsed between completion of first-line therapy and recurrence in 50% of patients. Thus, a similar time frame of 40 months between clinical complete response and the start of third-line therapies exists, which is comparable to results in GOG 178 (68).
- GOG 175: this trial evaluated 542 eligible patients who were staged IA or IB grade 3 or clear cell, all stage IC and all stage II ovarian cancer. They were all given IV carboplatin AUC 6 and paclitaxel 175 mg/m^2 for three cycles followed by randomization to either observation or weekly paclitaxel for 24 weeks. The 5Y recurrence probability rate was 23% for those observed, and 20% for those who received maintenance paclitaxel, HR 0.8. The 5 YS was 85.4% versus 86.2% (NS) (69).
- AGO-OVAR16: 940 patients with EOC, FIGO stages II–IV, and no evidence of progression after PDS and ≥5 cycles of platinum–taxane chemotherapy were randomized 1:1 to receive 800 mg pazopanib once daily, or placebo for up to 24 months. Of these, 91% had stage III/IV disease, 58% had no residual disease after surgery and 15% had *BRCA* 1/2 mutations. The primary endpoint was PFS by RECIST. Median follow-up was 24 months. Patients in the pazopanib arm had a prolonged PFS of 5.6 months versus placebo (HR 0.766; 95% CI: 0.64–0.91; $p = 0.0021$; The median PFS was 7.9 vs 12.3 months for pazopanib v placebo respectively). The first interim analysis for OS (only 189 OS events = 20.1% of population) showed no difference between arms. The median PFS was 30.3 in *BRCA* 1/2 carriers vs 14.1 months in the placebo arm (HR 0.48; 95% CI: 0.29–0.78; $p = 0.0031$). The median PFS in the pazopanib arm was 30.1 months vs 17.7 months with a HR of 0.64, (95% CI: 0.4–1.03; $p = 0.069$). Among *BRCA* 1/2 non carriers, the PFS was longer for those treated with pazopanib at 17.7 months compared to 14.1 months in the placebo arm (HR 0.77; 95% CI: 0.62–0.97; $p = 0.024$). Pazopanib mean exposure was shorter versus placebo (8.9 vs. 11.7 months). Pazopanib treatment was associated with a higher incidence of AEs and serious AEs (26% vs. 11%) versus placebo. The most common AEs were hypertension, diarrhea, nausea, headache, fatigue, and neutropenia. Fatal serious AEs were reported in three patients on pazopanib and one patient on placebo (70).
- Study 19: olaparib maintenance therapy. 256 patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen were included in this double blind phase II randomized study. *BRCA* 1/2 mutation status was not required

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but was known in 36.6% of patients at study entry. Olaparib was dosed at 400 mg twice daily. The primary endpoint was PFS. A total of 136 were assigned to the olaparib group and 129 to the placebo group. The PFS was significantly longer with olaparib than with placebo (median, 8.4 months vs. 4.8 months from randomization on completion of chemotherapy; HR for progression or death, 0.35; 95% CI: 0.25–0.49; $p < 0.001$). Subgroup analyses of PFS showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression. Adverse events reported in the olaparib group versus the placebo group were nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), and anemia (17% vs. 5%); the majority of AEs were grade 1 or 2. An interim analysis of OS (38% maturity, meaning that 38% of the patients had died) showed no significant difference between groups (HR with olaparib, 0.94; 95% CI: 0.63–1.39; $p = 0.75$). A subset analysis showed patients with mutations were most likely to benefit. There was an 82% reduction in risk of disease progression or death in mutation patients, translating to a median PFS of 11.2 months with drug compared to 4.3 months on placebo. OS data for mutation patients were 34.9 versus 31.9 months (NS). The highest benefit was seen in *BRCA*-mutation carriers with platinum sensitive disease (71).

- Solo-1: this is a phase III study testing olaparib as maintenance therapy following response to frontline platinum-based treatment in g*BRCA*-mutated FIGO stage III to IV surgically debulked ovarian cancer patients. This is a double-blind multicenter study in which patients are randomized (2:1) to receive olaparib (300 mg [2 × 150 mg tablets] BID) or placebo. Patients must have high-grade serous or endometrioid ovarian type cancer, including primary peritoneal and/or fallopian tube cancer, who have a known deleterious (or suspected deleterious) *BRCA*m and who are in complete or partial response following the completion of platinum-based chemotherapy. The primary objective is PFS by blinded independent central review using RECIST v1.1. Radiologic scans will be performed at baseline and every 12 weeks for 120 weeks, and every 24 weeks thereafter. Blinded treatment will continue until objective DP. Primary analyses will be performed at approximately 60% maturity using log-rank tests. Other objectives for both trials include: OS; time to earliest progression (RECIST or CA-125); time from randomization to second progression (PFS2); health-related quality of life (HRQOL); tolerability. Target recruitment: n is approximately equal to 344 randomized patients. Results pending.
- ARIEL3: this is a phase III trial designed to evaluate the effect of rucaparib as maintenance treatment following platinum-based therapy in women with platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer. The biomarker results from the ARIEL2 study will be applied to the analysis of results in this study. NCT01968213: results pending.
- AGO-OVAR 16: a phase III study evaluated the efficacy and safety of pazopanib monotherapy versus placebo in women who have not progressed after first-line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer. 940 patients were randomized 1:1 to receive either 800 mg of pazopanib once daily or placebo for up to 24 months. The median follow-up

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was 24.3 months. The median PFS was 17.9 months in the pazopanib arm and 12.3 months in the placebo arm (HR – 0.77; $p = 0.0021$). The interim survival analysis did not show any significant difference between the two study arms after events in 36.5% of the study population. In an exploratory analysis of ethnicity, pazopanib appeared to have superior benefit in the 78% of patients who were not of East Asian descent (HR – 0.69; median PFS benefit, 5.9 months), compared to 22% of patients of East Asian descent who had an HR of 1.16. Toxicity was high and treatment discontinuation occurred more often in the pazopanib arm: 33% of patients discontinued treatment compared with 5.6% of patients in the placebo arm. The incidence of grade 3 or 4 AEs was higher in the pazopanib arm: hypertension in 30.8%, neutropenia in 9.9%, liver-related toxicity in 9.4%, diarrhea in 8.2%, thrombocytopenia in 2.5%, and palmar–plantar erythrodysesthesia in 1.9%. Three patients in the pazopanib arm had a fatal AE—a myocardial infarction, pneumonia, and posterior reversible encephalopathy syndrome. One patient in the placebo arm had fatal acute leukemia (70).

- MANGO-2/ILIAD: this was a phase IV trial using biomarker data for ovarian cancer patients treated on study 55041 with bevacizumab and carboplatin followed by erlotinib maintenance versus observation in patients with no evidence of DP after first-line platinum-based chemotherapy. Somatic mutations in KRAS, BRAF, NRAS, PIK3CA, EGFR, and PTEN were determined in 318 (38%) and expression of EGFR, pAkt, pMAPK, E-cadherin and Vimentin, and EGFR and HER2 gene copy numbers in 218 (26%) of a total of 835 randomized patients. Biomarker data were correlated with PFS and OS. Only 28 mutations were observed among KRAS, BRAF, NRAS, PIK3CA, EGFR, and PTEN (in 7.5% of patients), of which the most frequent were in KRAS and PIK3CA. EGFR mutations occurred in only three patients. When all mutations were pooled, patients with at least one mutation in KRAS, NRAS, BRAF, PIK3CA, or EGFR had longer PFS (33.1 vs. 12.3 months; HR 0.57; 95% CI: 0.33–0.99; $p = 0.042$) compared to those with wild-type tumors. EGFR overexpression was detected in 93 of 218 patients (42.7%), and 66 of 180 patients (36.7%) had EGFR gene amplification or high levels of copy number gain. 58 of 128 patients had positive pMAPK expression (45.3%), which was associated with inferior OS (38.9 vs. 67.0 months; HR 1.81; 95% CI: 1.11–2.97; $p = 0.016$). Patients with positive EGFR fluorescence in situ hybridization (FISH) status had worse OS (46.1 months) than those with negative status (67.0 months; HR 1.56; 95% CI: 1.01–2.40; $p = 0.044$) and shorter PFS (9.6 vs. 16.1 months; HR 1.57; 95% CI: 1.11–2.22; $p = 0.010$). None of the investigated biomarkers correlated with responsiveness to erlotinib. Conclusion: increased EGFR gene copy number was associated with worse OS and PFS in patients with ovarian cancer (72).
- TRINOVA-3 AGO-OVAR 18: randomized phase III trial evaluating paclitaxel and carboplatin plus trebananib or placebo followed by trebananib or placebo maintenance for 18 months in the front-line therapy. Results pending.

- **Recurrent Disease Trials**
  - EORTC 55005: gemcitabine-carboplatin versus carboplatin: this trial evaluated platinum-sensitive relapsed ovarian cancer in 356 eligible patients. Single-agent carboplatin AUC 5 was compared to carboplatin AUC 4 with

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gemcitabine dosed at 1,000 mg/m^2 given on days 1 and 8, every 21 days. The PFS was improved with the addition of gemcitabine (8.6 months vs. 5.8 months HR 0.72 (95% CI: 0.58–0.90; p = 0.0031)). The study was not powered to detect a difference in OS. The ORR was 47% with the addition of gemcitabine versus 30% with single-agent carboplatin (HR 0.96; 95% CI: 0.75–1.23; p = 0.7349). 60% of patients recurred at greater than 12 months and 40% recurred between 6 months and 12 months (73).

- A randomized phase III study of pegylated liposomal doxorubicin (PLD) versus topotecan in recurrent EOC. This trial evaluated 474 patients with recurrent disease in response to single-agent therapy. Liposomal doxorubicin was dosed at 50 mg/m^2 every 4 weeks, and topotecan was dosed at 1.5 mg/m^2/day for 5 days every 3 weeks. The median survival for patients was 63 weeks for PLD versus 60 weeks for topotecan (HR 1.216; 95% CI: 1–1.478; p = 0.05). For those patients who had platinum-sensitive disease there was a significant difference in time until progression: 108 weeks versus 70 weeks, favoring PLD (HR 1.432; 95% CI: 1.066–1.923; p = 0.017). For patients with platinum resistant disease, OS was similar (74).
- OCEANS: this trial evaluated 484 eligible patients who received carboplatin AUC 4 and gemcitabine 1,000 mg/m^2 on days 1 and 8 with or without the addition of bevacizumab at 15 mg/kg IV every 3 weeks in recurrent platinum-sensitive disease. Six to 10 cycles were given with a median follow-up of 58.2 months in the bevacizumab arm and 56.4 months in the placebo arm. An ORR of 78.5% versus 57.4% was seen. Duration of response was 10.4 months versus 7.4 months (HR 0.534; 95% CI: 0.408–0.698), favoring the bevacizumab arm. The median OS was comparable between arms, with 33.6 months in the bevacizumab arm versus 32.9 months in the placebo arm (HR 0.95 log rank p = 0.65), thus no difference between arms. The PFS demonstrated a HR of 0.48, favoring the bevacizumab arm, with months until progression of 12.4 versus 8.4. Grade 3 HTN occurred in 17.4% of the experimental arm versus 1% with placebo. OS results were possibly confounded by extensive use of subsequent anticancer therapies (75,76).
- CALYPSO EORTC 55051: 976 patients in this international noninferiority trial with recurrent late relapsing (>6 months after first- or second-line platinum- and paclitaxel-based therapies) platinum-sensitive ovarian cancer were treated with the doublets of carboplatin AUC 5 and liposomal doxorubicin dosed at 30 mg/m^2 every 4 weeks (CD) versus the standard of carboplatin AUC 5 and paclitaxel 175 mg/m^2 for at least six cycles every 3 weeks (CP). 40% of patients had received two prior regimens before entering the study. A maximum of nine cycles were administered. The ORR was 63%, including 38% of patients who achieved a complete response. Patients in the CD arm had a better PFS of 11.3 months compared to the CP arm with 9.4 months (HR 0.82 (95% CI: 0.72, 0.94); p = 0.005)). The median survival times were 30.7 months and 33 months for the CD arm versus the CP arm (NS). CD led to delayed progression but similar OS compared to CP in platinum-sensitive ovarian cancer. In a subset analysis: patients with a tumor free interval > 24 months were analyzed separately. A total of 259

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very platinum-sensitive patients were included (n = 131, CD; n = 128, CP). The median PFS was 12.0 months for the CD arm and 12.3 months for CP (HR 1.05; 95% CI: 0.79–1.40; p = 0.73 for superiority) and median OS was 40.2 months for CD and 43.9 for CP (HR 1.18; 95% CI: 0.85–1.63; p = 0.33 for superiority). ORRs were 42% and 38%, respectively (p = 0.46). This subset analysis found that CP and CD were equally effective treatment regimens for patients with very platinum-sensitive recurrent ovarian cancer but the favorable risk-benefit profile suggested that carboplatin-PLD should be the treatment of choice for these patients due to better toxicity profiles (77,78).

- AURELIA trial (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) AGO-OVAR 2.15: 361 patients with platinum resistant disease following front line platinum chemotherapy were enrolled and randomly allocated to receive a single nonplatinum chemotherapy agent alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks). The nonplatinum chemotherapy agent was selected by the investigator from one of the following options: liposomal doxorubicin (PLD) 40 mg/m^2 q28 days; weekly paclitaxel at 80 mg/m^2; topotecan 1.25 mg/ m^2 on days 1 to 5 q3 weeks, or topotecan 4 mg/m^2 on days 1, 8, 15 q28 days. If patients progressed on the single agent chemotherapy arm, they were allowed to cross over to bevacizumab alone. The primary endpoint was PFS. Patients in the chemotherapy alone arm had a median PFS of 3.4 months vs 6.7 months with bevacizumab (HR 0.48, 95% CI: 0.38–0.60; $p < 0.001$). The RECIST ORR was 11.8% in the chemotherapy alone arm versus 27.3% in the group with bevacizumab added (p = 0.001). The HR for OS was 0.85 (95% CI: 0.66–1.08; $p < 0.174$). There was no statistically significant difference in OS between the chemotherapy regimens (HR 0.85; 95% CI: 0.66–1.08 unstratified log-rank $p < 0.174$). There was no statistically significant difference in OS between the regimens (HR 0.85; 95% CI: 0.66–1.08 unstratified log-rank $p < 0.174$). Crossover occurred in 40% of patients randomized initially to CT. The median OS was 13.3 months for chemotherapy versus 16.6 months for chemotherapy plus bevacizumab (95% CI: 13.7–19). Gastrointestinal (GI) perforation occurred in 2.2% of bevacizumab-treated patients. The QOL arm showed a greater than 15% improvement in abdominal/GI symptoms at weeks 8/9 with the addition of bevacizumab; 21.9% versus 9.3% difference. In a subset analysis of the chemotherapy alone cohort, there was found to be an extensive crossover from chemotherapy alone to bevacizumab (PLD, 39%; paclitaxel, 38%; topotecan, 41%), which complicated interpretation of the data. The PFS HRs were 0.57 (95% CI: 0.39–0.83) for PLD (median 5.4 vs. 3.5 months, favoring the addition of bevacizumab), 0.46 (95% CI: 0.30–0.71) in the paclitaxel cohort (median 10.4 vs. 3.9 months), and 0.32 (95% CI: 0.21–0.49) for the topotecan cohort (median 5.8 vs. 2.1 months). The overall response rate evaluable by RECIST criteria was greater in regimens that included bevacizumab compared to chemotherapy alone for all cohorts: PLD cohort 13.7% vs. 7.8% (95% CI: −7.2% to 19.0%); paclitaxel cohort 53.3% vs. 30.2% (95% CI: 1.7%–44.5%);

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topotecan cohort 17.0% vs. 0.0% (95% CI: 5.1%–28.9%). Gastrointestinal symptoms improved by 15% or more in each group that contained bevacizumab compared to chemotherapy alone: PLD cohort 21.1% versus 6.8%; paclitaxel cohort 25.0% versus 13.0%, and topotecan cohort 20.0% versus 8.8%. The unadjusted HRs for bevacizumab-containing chemotherapy versus chemotherapy alone were: HR 0.91 (95% CI: 0.62–1.36) for the PLD cohort (median 13.7 vs. 14.1 months); HR 0.65 for the paclitaxel cohort (95% CI: 0.42–1.02) (median 22.4 versus 13.2 months); and HR 1.09 (95% CI: 0.72–1.67) for the topotecan cohort (median 13.8 vs. 13.3 months). In the chemotherapy alone arms, progression, median PFS and ORR varied among groups. Topotecan was usually given weekly and seemed less active than weekly paclitaxel, whereas PLD had intermediate results. There was no difference in OS between treatment arms in the PLD and topotecan cohorts, but Kaplan–Meier curves for OS were clearly separated in the paclitaxel cohort; thus, a combination of paclitaxel and bevacizumab may enhance both of their antiangiogenic effects and potentially account for their better HRs in AURELIA (79,80).

- TRINOVA-1: this was a randomized, double-blind international phase III study in women with recurrent EOC evaluating trebananib in antiangiogenesis. 919 women were enrolled. Patient eligibility criteria included having been treated with three or fewer previous regimens, and a platinum-free interval of less than 12 months. Patients were randomly assigned to weekly IV paclitaxel (80 mg/m^2) plus either weekly masked IV placebo or trebananib (15 mg/kg). Patients were stratified on the basis of platinum-free interval (≥0 and ≤6 months vs. >6 and ≤12 months), presence or absence of measurable disease, and region. The primary endpoint was PFS. The median PFS in the trebananib arm was 7.4 months (95% CI: 7.0–7.8) versus 5.4 months (95% CI: 4.7–5.5) in the placebo arm (HR 0.70; 95% CI: 0.61–0.80; $p < 0.001$). The ORR was 29.8% versus 38.4% ($p = 0.0071$). The median OS was 19.3 months in the trebananib arm versus 18.3 months in the control arm (NS); (HR 0.95; 95% CI: 0.81–1.11; $p = 0.52$). In a subgroup analysis, trebananib improved the median OS compared with placebo (14.5 vs. 12.3 months; HR 0.72; 95% CI: 0.55–0.93; $p = 0.011$) in patients with ascites at baseline ($n = 295$). In the intent-to-treat population, trebananib significantly improved median PFS-2 compared with placebo (12.5 vs. 10.9 months; HR 0.85; 95% CI: 0.74–0.98; $p = 0.024$). PFS-2 confirmed that the PFS benefit associated with trebananib was maintained through the second DP, independent of the choice of subsequent therapy (81,82).
- TRINOVA-2 AGO-OVAR 2.19/ENGOT-OV-6: this was a randomized phase III trial evaluating PLD plus trebananib or placebo in patients with recurrent partially platinum-sensitive or -resistant disease that enrolled 223 patients. No subgroup of patients showed a favorable PFS with experimental treatment but those with baseline ascites treated with trebananib showed a trend toward improved PFS (HR 0.6; 95% CI: 0.35–1.04). Trebananib use was associated with an improved response rate but no improvement in OS (83).

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- ICON6: this was a three-arm, double-blind, placebo-controlled randomized trial using the oral VEGFR-1,2,3 inhibitor, cediranib, in relapsed platinum sensitive ovarian cancer. 456 patients were enrolled with a median age of 62 years. Previous treatment interval greater than 12 months (67%) was balanced between arms. The primary endpoint was PFS. Patients were randomized 2:3:3 for up to six cycles of platinum-based chemotherapy with either placebo, cediranib 20 mg/day during chemotherapy (paclitaxel/carboplatin, gemcitabine/carboplatin, or single agent carboplatin) followed by placebo for up to 18 months (concurrent) or cediranib 20 mg/day followed by maintenance cediranib (concurrent + maintenance). Cediranib plus platinum-based chemotherapy followed by maintenance cediranib provided a benefit compared to chemotherapy alone, with an improved PFS from 9.4 to 12.5 months and an improved OS by 2.7 months (17.6–20.3 months HR 0.7; log-rank test $p = 0.0419$). PFS comparing reference and concurrent plus maintenance using a log-rank test gave a p-value of 0.00001 with an associated HR of 0.57 (95% CI: 0.45–0.74). However, because of nonproportional hazards ($p = 0.0237$ for PFS and $p = 0.0042$ for OS) the HR can be difficult to interpret, and instead survival time was estimated using restricted means (RM) and HRs were given for completeness. The RM estimates an increased time to progression of 3.2 months from 9.4 to 12.6, during 2 years. Similarly using RM, OS increased by 2.7 months from 17.6 to 20.3 (HR 0.70; log-rank test $p = 0.0419$). PFS using RM for the reference versus concurrent arms saw an increase of 2.0 months from 9.4 to 11.4 months (HR 0.68; log-rank test $p = 0.0022$). AEs significantly more common in the cediranib-maintenance arm were: hypertension, diarrhea, hypothyroidism, hoarseness, hemorrhage, proteinuria, and fatigue (84).
- NOVA trial: **N**iraparib **OVA**rian trial (MK-4827): this was a double blind, placebo-controlled phase III trial of niraparib. 490 patients with high-grade serous, platinum-sensitive, relapsed ovarian cancer were enrolled into one of two independent cohorts based on germline *BRCA* mutation status. Cohort 1 was germline *BRCA* mutation carriers (g*BRCA*mut), and cohort 2 was those who were not germline *BRCA* mutation carriers (non-g*BRCA*mut). The non-g*BRCA*mut cohort included patients with homologous recombination deficiency (HRD)-positive tumors, including those with somatic *BRCA* mutations and other HR defects, and patients with HRD-negative tumors. Within each cohort, patients were randomized 2:1 to receive niraparib or placebo and were treated continuously with placebo or 300 mg of niraparib until progression. Among patients who were germline *BRCA* mutation carriers, the niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with an HR of 0.27. The median PFS for patients treated with niraparib was 21.0 months, compared to 5.5 months for control ($p < 0.0001$). For patients who were not germline *BRCA* mutation carriers but whose tumors were determined to be HRD positive using the Myriad myChoice® HRD test, the niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with an HR of 0.38. The median PFS for patients with HRD-positive tumors who were treated with niraparib was 12.9 months, compared to 3.8 months for control ($p < 0.0001$).

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A statistical significance in the overall nongermline *BRCA* mutant cohort was also seen for niraparib, which included patients with both HRD-positive and HRD-negative tumors. The niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with an HR of 0.45. The median PFS for patients treated with niraparib was 9.3 months, compared to 3.9 months for control ($p < 0.0001$). The most common grade 3/4 AEs were thrombocytopenia (28.3%), anemia (24.8%), and neutropenia (11.2%). The discontinuation rate was 14.7% for niraparib-treated patients and 2.2% for control. The rates of myelodysplastic syndrome/acute myelogenous leukemia in the niraparib (1.3%) and control (1.2%) arms were similar. There were no deaths among patients during study treatment (85).

- OVA-301: in a phase III randomized trial, trabectedin plus PLD in recurrent ovarian cancer resulted in a 35% risk reduction of disease progression or death (HR 0.65, 95% CI: 0.45–0.92; $p = 0.0152$). 337 patients were randomized to the combination trabectedin/PLD arm vs 335 patients randomized to the PLD arm. The median PFS was 7.4 versus 5.5 months. There was a 41% decrease in the risk of death (HR 0.59; 95% CI: 0.43–0.82; $p = 0.0015$). The median survival was 23.0 versus 17.1 months favoring the trabectedin arm. Similar proportions of patients received subsequent therapy in each arm (76% vs. 77%), although patients in the trabectedin/PLD arm had a slightly lower proportion of further platinum (49% vs. 55%). Importantly, patients in the trabectedin/PLD arm survived significantly longer after subsequent platinum (HR 0.63; $p = 0.0357$; median 13.3 vs. 9.8 months). This hypothesis-generating analysis demonstrates that superior benefits with trabectedin/PLD in terms of PFS and survival in the overall population appear particularly enhanced in patients with partially sensitive disease (PFI 6–12 months) (86).
- MITO 11: this was an open-label, randomized phase II trial addressing the effect of adding pazopanib to paclitaxel for patients with platinum-resistant or platinum-refractory advanced ovarian cancer. Patients previously treated with a maximum of two lines of chemotherapy, ECOG PS 0–1, and no residual peripheral neurotoxicity were randomly assigned (1:1) to receive weekly paclitaxel 80 mg/m^2 with or without pazopanib 800 mg daily, and stratified by center, number of previous lines of chemotherapy, and platinum-free interval status. The primary endpoint was PFS, assessed in the modified intention-to-treat population. 74 patients were enrolled: 37 were assigned to receive paclitaxel and pazopanib and 37 assigned to paclitaxel only. The median follow-up was 16.1 months (IQR 12.5–20.8). The PFS was significantly longer in the pazopanib plus paclitaxel group than in the paclitaxel only group (median 6.35 months [95% CI: 5.36–11.02] vs. 3.49 months [2.01–5.66]; HR 0.42 [95% CI: 0.25–0.69]; $p = 0.0002$). No unexpected toxic effects or deaths were recorded. AEs were more common in the pazopanib and paclitaxel group to include neutropenia (30% vs. 3%], fatigue (11% vs. 6%), leucopenia (11% vs. 3%), and hypertension (8% vs. 0%). One patient in the pazopanib group had a small bowel perforation. The PFS was 6.3 versus 3.5 months (HR 0.42, 95% CI: 0.25–0.69). The RR was 50% versus 21% ($p = 0.03$) (87).
- GOG 26FF: this phase II study evaluated single-agent paclitaxel at 170 mg/m^2 IV over 24 hours every 3 weeks in 43 refractory or platinum-resistant ovarian

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cancer patients. The ORR was 37%. The median PFI was 4.2 months, the median survival was 16 months. PFS was 4 months (88).

- GOG-186F: this was a phase II study that estimated the activity of docetaxel 60 mg/m^2 IV over 1 hour followed by trabectedin 1.1 mg/m^2 over 3 hours with filgrastim, pegfilgrastim, or sargramostim every 3 weeks. 71 patients with recurrent and measurable disease, PS ≤ 2, and ≤3 prior regimens were eligible. A historical GOG taxane control study was used for direct comparison. The goal of this study was to determine if the trabectedin regimen had an RR of ≥36% with 90% power. The median number of cycles given was six (438 total cycles, range 1–22). The number of patients responding was 21 (30%; 90% CI: 21%–40%). The OR for responding was 2.2 (90% 1-sided CI: 1.07–∞). The median PFS and OS were 4.5 months and 16.9 months, respectively. The median duration of response was 6.2 months (89).
- GOG 186i: 107 women with recurrent platinum sensitive or resistant EOC treated with one to three prior chemotherapy lines were randomized to bevacizumab or bevacizumab with fosbretabulin (a vascular disrupting agent). PFS was improved to 7.3 versus 4.8 months (HR 0.69; 95% CI: 0.47–1 at 90%). Response rates were 36% versus 28%. Although not a statistically significant result, patients receiving the combination had an ORR of 35.7% ($n = 42$) compared to 28.2% for patients on bevacizumab alone ($n = 39$). The study achieved its primary endpoint and demonstrated a statistically significant increase in PFS for the combination as compared to bevacizumab alone ($p = 0.049$; HR 0.685). In a post-hoc subgroup analysis, data showed that in patients who were platinum resistant, the addition of fosbretabulin to bevacizumab increased the ORR to 40% ($n = 10$) compared to 12.5% ($n = 8$) for bevacizumab. Among those patients, the median PFS was 6.7 months for those on bevacizumab and fosbretabulin compared to 3.4 months for those receiving bevacizumab alone ($p = 0.01$; HR 0.57). Patients in the combination arm experienced an increased incidence of G3 HTN compared to the control arm (90).
- GOG186j: this phase II trial evaluated weekly paclitaxel ± pazopanib in women with recurrent EOC and one to three lines of prior chemotherapy. 100 women were analyzed and PFS was the primary endpoint. Compared to weekly paclitaxel there was no significant difference in PFS: the median was 7.5 versus 6.2 months (HR 0.84; 90% CI: 0.57–1.22) in the combination versus single-agent group. The RR was 32% versus 23%, respectively. HTN was more common in the combination arm and lead to treatment discontinuation in 37% versus 10% of the paclitaxel-only arm. More patients progressed on the control arm at 65% versus 32% (91).
- Veliparib in *BRCA*m relapsed ovarian cancer patients. In this phase II study, 50 patients were evaluated of whom 60% were platinum resistant. The median number of cycles was six. Veliparib was administered at 400 mg BID with a cycle length of 28 days. The ORR was 26%; 3 patients had a CR, and 11 patients had a partial response (PR). Platinum-resistant patients had a 20% RR, and platinum-sensitive patients had a 35% RR. The median PFS was 8.2 months (92).

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- AGO-OVAR 2.20: PENELOPE trial: a two-part randomized phase III double blind trial evaluating pertuzumab in combination with standard chemotherapy in women with recurrent platinum-resistant EOC and low HER3 mRNA expression. 156 patients were randomized to pertuzumab or placebo. Pertuzumab was administered at 840 mg IV loading dose followed by q21 day dosing at 420 mg IV in combination with either paclitaxel at 80 mg/m^2 on days 1, 8, 15 every 3 weeks or gemcitabine 1,000 mg/m^2 on days 1, 8 every 3 weeks, or topotecan 1.25 mg/m^2 on days 1 to 5 every 3 weeks. PFS was 4.3 months for pertuzumab plus chemotherapy versus 2.6 months for placebo for chemotherapy. PFS was extended in the paclitaxel (most pronounced) and gemcitabine cohorts specifically and further exploration of this agent in combination regimens can be explored. A longer PFS was also seen in those with no prior antiangiogenic therapy (93).
- Combination cediranib and olaparib versus olaparib alone; this was a randomized phase II study of women with recurrent platinum-sensitive ovarian cancer. 46 women received olaparib at 400 mg PO BID and 44 received combination therapy with olaparib dosed at 200 mg PO BID with cediranib 30 mg PO daily. The median PFS was significantly longer with cediranib/olaparib compared with olaparib alone (17.7 vs. 9.2 months; HR 0.42; $p = 0.005$). In a subset analysis of g*BRCA* mutation status, a significant improvement in PFS in g*BRCA* wild-type or unknown patients receiving cediranib–olaparib compared with olaparib alone (16.5 vs. 5.7 months; $p = 0.008$) with no significant improvement in PFS observed in the g*BRCA* patients (19.4 vs. 16.5 months; $p = 0.16$) (94,95).
- Cediranib in recurrent or persistent ovarian, peritoneal, or fallopian tube cancer: this was a phase II trial of cediranib dosed at 30 mg daily. 74 patients were evaluated: 39 were platinum sensitive (Pl-S) and 35 were platinum resistant (Pl-R). For those who were Pl-S, 26% had a PR and 51% had stable disease (SD). In the Pl-R arm there were no PR but 66% had SD. The median PFS for all patients was 4.9 months, for the Pl-S patients the PFS was 7.2 months and for the Pl-R patients, the PFS was 3.7 months. The median OS was 18.9 months, 27.7 for the Pl-S and 11.9 for the Pl-R patients (96).
- SOLO-2: 295 germline *BRCA* 1/2 mutant patients with platinum sensitive (2 or more prior platinum therapies in PR or CR) relapsed EOC were randomized 2:1 in a phase III trial to treatment with olaparib 300 mg BID compared to placebo maintenance therapy. The olaparib arm had a 19 month DFS compared to the placebo arm at 5.5 months (HR 0.3, 95% CI: 0.22–0.41, $p < 0.0001$). PFS in the olaparib arm was 30.2 months compared to 5.5 months in the placebo arm (HR 0.25, 95% CI: 0.18–0.35, $p < 0.0001$). A benefit in time to second progression or death was also seen (HR 0.50 95% CI: 0.34-0.72, $p = 0.0002$) with the median not reached compared to 18.4 months. Grade 3 Adverse events were identified in 36.9% of patients on the olaparib arm compared to 18.2% in the placebo arm. 75.6% had nausea compared to 2.6% in the placebo arm (136).
- ARIEL2 (Assessment of Rucaparib In Ovarian Cancer Trial): this phase II study for patients with relapsed, high-grade, platinum-sensitive ovarian cancer evaluated the clinical activity of rucaparib dosed at 600 mg BID in

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3 pre-determined HRD subgroups: *BRCA* mutated (germline or somatic), *BRCA* wild-type/ loss of heterozygosity (LOH) high and *BRCA* wild-type/ LOH low. The primary endpoint for the study was progression free survival. Median PFS was 12.8 months (95% CI: 9.0-14.7) in the *BRCA* mutated group, 5.7 months (5.3–7.6) in the *BRCA* wild-type/LOH high group, and 5.2 months (3.6-5.5) in the *BRCA* wild-type/LOH low subgroup. *BRCA* mutated (HR 0.27, 95% CI: 0.16–0.44, $p < 0.0001$) and *BRCA* wild-type/ LOH high (0.62, 0.42–0.90, $p = 0.011$) groups had a significantly longer progression free survival than the *BRCA* wild-type/LOH low subgroup. Anemia (22% patients) and elevated liver enzymes (12%) were the 2 most common grade 3 side effects. Interim results identified robust activity with a 65% ORR in patients with a germline *BRCA* mutation and improved RR of 36% in *BRCA* wild type patients with homologous recombination deficiency measured by high loss of heterozygosity in tumors (97).

- DESKTOP I (Descriptive Evaluation of Preoperative Selection KriTeria for OPerability): 267 platinum-sensitive recurrent ovarian cancer patients were retrospectively reviewed for predictability of secondary cytoreduction. Complete secondary resection was associated with longer survival compared to any residual postoperative disease (45.2 vs. 19.7 months). Variables associated with complete resection were: performance status, early-stage FIGO disease (I/II), residual disease left after primary surgery (none vs. any), absence of ascites, and less than 500 mL of ascites. A combination of good PS, early FIGO stage, no residual disease, and absent ascites predicted complete resection in 79% of patients (98).
- DESKTOP II AGO-OVAR OP.2: This trial evaluated 516 recurrent platinum-sensitive ovarian cancer patients. Patients were screened with the DESKTOP I prediction factors for operability for recurrent disease: (a) complete resection at first surgery, (b) good performance status, and (c) absence of ascites. The DESKTOP II trial was intended to verify the DESKTOP I trial. 51% were classified as score positive; of these 261 patients, 129 were operated on. The rate of complete resection was 76%, confirming score validity and; 11% had second operations for complications (99).
- GOG 254: sunitinib evaluation in the treatment of persistent or recurrent clear cell ovarian cancer: 30 patients were treated in this phase II trial of sunitinib 50 mg per day for 4 weeks administered in repeated 6-week cycles until DP or toxicity. 6.7% had a PR or CR. The median PFS was 2.7 months. The median OS was 12.8 months. There was minimal activity in second- and third-line treatment in recurrent clear cell ovarian cancer (100).
- Volasertib in platinum resistant or refractory ovarian cancer: 109 patients were randomized to single agent investigator chosen nonplatinum chemotherapy (PLD, topotecan, paclitaxel, or gemcitabine) or volasertib (an inhibitor of Polo-like kinases) at 300 mg IV q21 days until disease progression or toxicity. The primary endpoint was 24-week disease control rates. The disease control rate for volasertib was 30.6% versus 43.1% for chemotherapy. Median PFS was 13.1 versus 20.6 weeks favoring chemotherapy. 11% of patients receiving volasertib had a durable response rate with PFS more than 1 year, and none had that response rate with chemotherapy. Thus, single

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agent volasertib has shown antitumor activity in this ovarian cancer patient population (101).

- FANG vaccine: this was a phase II trial consisting of 331 women who achieved a CCR with standard adjuvant chemotherapy. Patients were randomized 2:1 to receipt of an autologous tumor-based vaccine product incorporating a plasmid encoding granulocyte-macrophage colony-stimulating factor (GMCSF) and a novel bifunctional short hairpin ribonucleic acid (bi-shRNAi) targeting furin convertase, thereby downregulating endogenous immunosuppressive transforming growth factors (TGF) β1 and β2. Patients with advanced cancer received up to 12 monthly intradermal injections of FANG vaccine (1×10^7 or 2.5×10^7 cells/mL injection). GMCSF, TGFβ1, TGFβ2, and furin proteins were quantified by enzyme-linked immunosorbent assay (ELISA). PFS was 19.3 in the vaccine group versus 12.4 months in the observation group and saw an improved 3Y recurrence rate of 90% versus 60%. The researchers harvested cells from the tumor removed during the initial surgery to develop the personalized immunotherapy. Patients assigned the vaccine then received 1×10^7 cells/intradermal injection monthly for up to 12 doses. Researchers evaluated T-cell activation per interferon-gamma enzyme-linked immunospot assay (ELISPOT). A greater proportion of patients who were chemotherapy-naive achieved interferon-gamma ELISPOT response in the current analysis compared with the previous phase I trial (92% vs. 50%) (102).
- **INOVATYON trial:** a phase III clinical trial of recurrent platinum-sensitive ovarian cancer [identifier: NCT01379989] comparing Arm A: PLD 30 mg/m^2 with carboplatin AUC 5 to Arm B: PLD 30 mg/m^2 and trabectedin 1.1 mg/m^2. Accruing.

- **Interval Debulking Trials**
  - EORTC 44865: this trial randomized 319 patients with stage III and IV after suboptimal surgery to chemotherapy with cyclophosphamide and cisplatin for six cycles or to chemotherapy with cyclophosphamide and cisplatin for three cycles with interval debulking followed by three more cycles. The interval debulking group had a significantly better median PFS of 18 months versus 13 months. The median OS was 26 months versus 20 months, favoring the interval debulking group. The risk of death decreased by 33%, $p = 0.008$ (103).
  - GOG 152: this trial randomized 424 eligible patients stage III and IV after suboptimal surgery to chemotherapy with cisplatin and paclitaxel for six cycles or to chemotherapy for three cycles with interval debulking, followed by three more cycles of chemotherapy. The median PFS was 10.5 months versus 10.7 months (HR 1.07; 95% CI: 0.869 to 1.31; $p = 0.54$). The OS was 33.7 in the chemotherapy alone group compared to 33.9 months in the IDS group. The RR for death was 0.99 (95% CI: 0.786–1.24; $p = 0.92$) (104).

There were differences between the two preceding interval debulking studies. Namely, there was a more effective second-line therapy (paclitaxel) in the GOG study, the chemotherapy regimens were different, residual disease was 5 cm or less for fewer than two thirds of patients in GOG 152 versus one third of patients in the EORTC study, and generalists did a majority of the primary surgery in the EORTC study. Furthermore, residual disease after three cycles of chemotherapy was greater

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than 1 cm in 65% of patients in the EORTC study, thus there was an increased chance of optimal cytoreduction in the EORTC study, compared to only 45% who were converted to optimal debulking in the GOG study.

- GOG 213: this was a phase III randomized study with two primary objectives: (a) to examine the role of bevacizumab at 15 mg/kg in combination with paclitaxel at 175 mg/m^2 and carboplatin AUC 5 followed by bevacizumab maintenance, and (b) to examine the role of secondary cytoreduction before initiation of chemotherapy in recurrent patients. The primary endpoint was OS. Secondary endpoints were safety toxicity, allergy, PFS, and QOL. 674 patients were randomized. Prior bevacizumab was received in 67/606 patients. The median age was 60. For the chemotherapy arm: CTB combination chemotherapy improved the HR of death by 18.6% (HR 0.827; 95% CI: 0.683–1.005; $p = 0.056$) with a median OS of 42.2 versus 37.3 months. The PFS was improved with CTB with an HR 0.614 (95% CI: 0.522–0.722; $p < .0001$) with median PFS 13.8 versus 10.4 months. It extended the OS to 42.2 months versus 37.3 months but the p-value was NS at 0.056. Estimated completion for the surgical debulking arm is March 2019 (105).
- DESKTOP III AGO-OVAR OP.4: a randomized multicenter study to compare the efficacy of additional tumor surgery versus chemotherapy alone in recurrent platinum-sensitive ovarian cancer. The AGO-score was used to select patients with a less than 30% risk of ending with residual tumor after surgery for recurrent disease to avoid including patients who would not benefit from an operation. The goal of this study was to evaluate whether maximum effort of cytoreductive surgery followed by platinum-based combination chemotherapy improved OS compared to platinum-based combination chemotherapy alone in AGO-score positive patients. Primary outcome was OS in patients with platinum-sensitive recurrent ovarian cancer with a positive AGO-score. Secondary outcome measures: QOL and PFS. Results pending.
- SOCceR-1 trial: this is a multicenter randomized trial for women with first recurrence of FIGO stage IC to IV platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. First line treatment must have consisted of optimal (≤1 cm) cytoreductive surgery and (neoadjuvant) platinum/taxol-based chemotherapy. Inclusion criteria are: ascites < 500 mL (pocket < 8 cm on ultrasound examination), and the potential for R0 status after secondary cytoreduction, and a ECOG PS 0–1. First recurrence is defined as clinical and radiological signs of recurrence (RECIST 1.1 criteria) or elevated CA 125 (GCIG criteria). Participants were randomized between the standard of at least six cycles of IV platinum-based chemotherapy without secondary debulking surgery or versus the experimental treatment of secondary cytoreductive surgery followed by at least six cycles of IV platinum-based chemotherapy. The primary outcome measure was PFS. Results pending (106).
- Surgery in Ovarian Cancer Quality of life Evaluation Research study (SOCQER 1): SOCQER 1 was a single institution prospective evaluation of QOL following primary PDS or IDS in 93 women, 24 of whom had extensive ovarian cancer surgery, 32 who had standard ovarian cancer surgery (based on Aletti Surgical Complexity Score of 3 or lower) compared to 32 patients who had surgery for benign indications. These were reviewed at sequential

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time points. The cohort undergoing extensive surgery had deterioration in the immediate and short term QOL measures. But by 9 months scores in all three cohorts were equal (107).

- **Neoadjuvant Therapy Trials**
  - EORTC 55971: this trial evaluated 632 eligible patients who were staged IIIC or IV. They were randomized to upfront debulking surgery versus three cycles of neoadjuvant platinum-based chemotherapy followed by interval surgery and subsequent chemotherapy. Inclusion criteria were biopsy-proven ovarian cancer, in combination with a pelvic mass, the presence of metastases of ≥2 cm outside the pelvis, and a CA-125: CEA ratio ≥25. The median follow-up was 4.8 years. Baseline characteristics for Arms A and B were, respectively: median largest metastasis, 80/80 mm; FIGO stage IIIC, 76%/76%. The largest residual tumor was ≤1 cm in 48% after PDS (Arm A) and 83% after IDS (Arm B). Complications of PDS and IDS were: postoperative mortality 2.7%/0.6%; sepsis 8%/2%; grade 3/4 and hemorrhage 7%/4%. The PFS was 11 months in both arms (HR 0.99; 95% CI: 0.87–1.13). An OS of 29 and 30 months was seen for Arms A and B (HR 0.98; 95% CI: 0.85–1.14) (95).

    Some critics suggest that this OS is still less than the 36 months seen in the carboplatin/paclitaxel arm of GOG 111 evaluating suboptimally debulked ovarian cancer. Regarding neoadjuvant therapy versus PDS: the overall PFS was similar for both arms, approximately 12 months. OS was 30 versus 29 months overall. For those with R0 disease, OS was 38 versus 45 months, R1 disease 27 versus 32 months, R2 disease 25 versus 26 months.
  - MRC CHORUS trial: this study attempted to confirm the results of EORTC 55971. In this study, 550 patients with clinical FIGO stages III to IV ovarian cancer were randomized to surgery followed by six cycles of chemotherapy or NACT. The median age was 65, the median tumor size was 8 cm, 25% were stage IV, and 19% had a WHO PS of 2. There was a well-balanced randomization. In the intent-to-treat analysis, a median OS of 22.8 months for PDS was observed versus 24.5 months for NACT (HR 0.87; 95% CI: 0.76–0.98) favoring NACT. The median PFS was 10.2 versus 11.7 months (HR 0.91; 95% CI: 0.81–1.02) (108).
  - Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? 670 patients from EROTC 55971 were reviewed. These patients had been randomly assigned to PDS or neoadjuvant chemotherapy. Clinical factors were reviewed for those who could benefit more from the differing primary approaches. The size of the largest metastatic tumor and clinical stage were significantly associated with the magnitude of the benefit from treatment in terms of 5 YS. Stage IIIC patients with tumors less than 4.5 cm benefited more from PDS whereas stage IV patients with metastatic tumors greater than 4.5 cm benefited more from neoadjuvant chemotherapy. Primary outcome was OS. The potential 5 YS in the population of treated patients would be 27.3%, 7.8% higher than if all were treated with primary surgery, and 5.6% higher than if all were treated with neoadjuvant chemotherapy (109).
  - A meta-analysis suggests that, for each extra cycle of neoadjuvant chemotherapy, there is a 4.1-month decrease in survival. Within this meta-analysis,

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each 10% increase in cytoreduction yielded a 5.5% median increase in survival time, which equates to 3 months (10).

- SCORPION trial: this was a phase III trial evaluating 110 patients randomized to either PDS followed by adjuvant chemotherapy or NACT followed by IDS. Patients were triaged preoperatively to laparoscopic staging to assess tumor load. Tumor load was documented as a Fagotti score. 45.5% of the PDS patients had R0 status postoperatively compared to 57.7% of those who received NACT; $p = 0.206$. 52.7% of the patients in the PDS arm had grade 3–4 complications compared to 5.7% in the IDS arm, $p = 0.0001$ (110–112).
- Neoadjuvant chemotherapy has also been found to not improve the rate of complete resection or affect the morbidity of IDS in another study. This retrospective study reviewed 200 patients in separate cohorts based on year of diagnosis. Cohort 1 was those diagnosed from 2009 to 2011 with PDS; cohort 2 was those diagnosed after 2011 to 2013 (at publication of EORTC Vergote) and they underwent visceral-peritoneal debulking after three cycles of neoadjuvant chemotherapy. Patients with complete response or progressive disease never underwent surgical resection. Patients had diagnostic laparoscopy before debulking to evaluate for small bowel serosal disease or porta hepatic encasement. If no small bowel or porta hepatic involvement, conversion to laparotomy and debulking was attempted. Debulking was completed in 90% of patients in both groups. There was no difference in operating room times, estimated blood loss, hospital stay, or postoperative complications between cohorts (113).
- Yet another study shows that PDS should be the primary management approach for advanced EOC. Those who had NACT were more likely to have no residual disease (50.1% vs. 41.5%). The 7 YS for PDS was found to be 41% versus 8.6% if NACT was used. For those who obtained R0 at PDS, the 7 YS was 73.6% versus 21%. Those who had PDS with R0 status and had IP chemotherapy had a 7 YS of 90% (114).
- Summation of OS and PFS in seminal NACT, IP, and PDS trials.
  - JGOG Dose-dense* paclitaxel versus conventional q21 days dosing:
    - OS 100.5 versus 62.2 months
    - PFS 28.2 months versus 17.5 months
  - GOG 172 IP* versus IV dosing
    - OS 65.5 versus 49.7 months
    - PFS 23.8 months versus 18.3 months
  - Landrum's review on GOG 114/172 data on R1/R0 patients IP* versus IV
    - OS 43.2 months versus 20.1 months
    - PFS 100 months versus 50.9 months
  - Chan's GOG 262 dose dense paclitaxel versus q21 day with bevacizumab
    - PFS 14.7 months versus 14 months overall. But subgroup analysis:
      - 14.2 months versus 10.3 months dose dense* no bevacizumab
      - 14.9 months versus 14.7 months dose dense plus bevacizumab
  - Vergote's EORTC neoadjuvant versus PDS* both using q21 day dosing
    - PFS similar: both around 12 months
    - OS is similar at 30 months neoadjuvant versus 29 months PDS, but see the following for subgroup analysis by R status

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- R0: 38 months versus 45 months favoring PDS
- R1: 27 months versus 32 months favoring PDS
- R2: 25 months versus 26 months

- **Translational Studies**:
  - OVCAD study: "Ovarian Cancer—Diagnosis of a Silent Killer" is a study aimed to investigate new predictors for early detection of minimal residual disease in EOC. In this study, 275 consecutive patients with EOC were included and their clinical outcomes with regard to pathology, surgery, and chemotherapy were reviewed. Evaluable patients had stage II to IV cancer who underwent cytoreductive surgery, adjuvant platinum-based chemotherapy and had tissue specimens collected. Characteristics of the patients included the following: median age of diagnosis was 58 years, 94.5% Stage III/IV, 96% grade 2/3, 86% with serous histology, 67.6% with peritoneal implants, 76% with ascites, 52% with positive lymph nodes. The majority of patients underwent a bilateral salpingo-oophorectomy (90.9%) and omentectomy (92.4%); 77.3% underwent hysterectomy. 37.7% patients had a resection of the large bowel while 13.4% of patients had a small bowel resection. 69.5% of patients had a pelvic lymph node dissection and 66.9% underwent para aortic lymph node dissection. "Macroscopic" cytoreduction was achieved in 68.4%. Platinum-based chemotherapy was used in 98.2% of the patients. At the time of median follow up (37 months), 70 patients (25.5%) had platinum resistant recurrent disease. Results from this trial are being used in a myriad of other reviews (115).

OVARIAN TUMORS OF LOW MALIGNANT POTENTIAL (LMP): BORDERLINE TUMORS

CHARACTERISTICS

- LMP tumors represent 5% to 15% of ovarian malignancies. The median age at diagnosis ranges from 39 to 45 years old. 20% of these tumors are diagnosed at stage III or IV. There are no known risk factors.
- Clinical features include a mass, abdominal pain, bloating, abdominal distension, early satiety, dyspepsia, and an elevated CA-125.
- The route of spread is often transcoelomic, and can be lymphatic.
- Prognostic factors are stage, residual tumor, the presence of invasive implants, and micropapillary histology.

HISTOLOGY

- Pathologically, there is the absence of stromal invasion and the tumors have at least two of the following: nuclear atypia, mitotic activity, pseudostratification, and epithelial budding. There are two main histologic types: serous and mucinous. If foci are found of stromal invasion measuring 3 to 5 mm or 10 mm^2, the tumor is considered microinvasive. Outcomes for microinvasive tumors are usually favorable and parallel LMP tumors. If a mucinous borderline tumor is found to have three or more layers of epithelial cell stratification, it is considered

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a carcinoma. There is guidance from WHO that LMP tumors may represent the early part of the disease spectrum for invasive tubo-ovarian carcinomas.

- Frozen section diagnosis of borderline tumors can be difficult. In one study of patients with a final diagnosis of LMP tumor, 10% were diagnosed as having invasive cancer and 25% were reported to have benign cystadenomas on intraoperative frozen section. Therefore, the sensitivity of the frozen section analysis for LMP's was 65% (95% CI: 55%, 75%) (116). Size greater than 8 cm, micropapillary, endometrioid, or clear cell carcinoma histologies can contribute to this difficulty.
- The micropapillary subtype is a distinct entity and carries an adverse prognosis. *BRAF* mutations are commonly found in this subtype. The distinguishing architecture is a height-to-width ratio of 5:1. It is often associated with invasive implants. Micropapillary histology has a higher rate of recurrence at 26%.
- Serous LMP tumors represent 62% of all LMP tumors; 30% are diagnosed as stage I, and they are often bilateral; 10% to 20% have invasive implants.
- Mucinous LMP tumors represent about 38% of LMP tumors and 80% to 90% are found as stage I; 5% are bilateral. There is a greater malignant potential with these tumors than with the serous LMP tumors.
- Invasive implants are a major factor in determining whether to treat with adjuvant therapies or not. The 7Y OS for patients with noninvasive implants is 96%, and for those with invasive implants, 66%. The risk of invasive implants accompanies histology: for serous borderline tumors the risk is 6%, but increases to 49% with micropapillary tumors.

PRE-TREATMENT WORKUP

- Workup is the same as for TOC.

STAGING

- Staging is the same as for TOC. Contralateral tubo-ovarian and uterine conservation may be considered in patients considering future fertility with completion surgery after childbearing.

TREATMENT

- Treatment is primarily surgical and follows the same directives as those for malignant ovarian cancer: complete surgical staging with full cytoreduction to microscopic disease status.
- Fertility sparing treatment is a reasonable option if desired. A cystectomy or unilateral salpingo-oophorectomy (USO) can be performed with additional staging LND, biopsies, and omentectomy. The recurrence rate overall is 12%. If a cystectomy is performed, the recurrence rate is 23%, compared to 8% with a USO. The median time to recurrence is 2.6 years after a cystectomy and 4.7 years after a USO.
- If surgical staging was not performed or this was an incidental pathologic finding, there are data to suggest that repeat staging is not beneficial in this patient

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population, given that no micropapillary histology is present. One series (116) compared early-stage LMP tumors in 31 staged patients to 42 unstaged patients ($p = 0.01$). 17% of patients had their stage upgraded based on surgical staging, but 5Y OS was 93% for all stages. The OS was similar in both groups. LN positivity made no difference in OS. Oftentimes endosalpingiosis is seen in the LN.

- Adjuvant chemotherapy should be considered if there are invasive implants. Treatment usually includes adjuvant chemotherapy that is platinum based. There is an average 25% response rate for LMP tumors to chemotherapy. At second look, the response to chemotherapy was 15% if noninvasive implants were present, versus 57% if invasive implants were present, thus borderline tumors are not completely chemoresistant (117).

RECURRENCE

- Recurrence in a spared contralateral ovary can occur in 16%–23% of patients, but is treated by resection of the tube and ovary. There were no deaths in those managed conservatively.
- Recurrent disease is often indolent. Recommended treatment is repeat cytoreduction. Overall, 5% to 10% of tumors recur. There are data to suggest that 73% recur as low-grade invasive cancers (118).

SURVIVAL (Table 2.11)

Table 2.11 LMP Ovarian Cancer 10Y Survival by Stage

Stage	Relative 10Y survival (%)
I	99
II	98
III	96
IV	77

LMP, low-malignant potential.

SURVIVAL CARE

- Follows the same pattern as that of HGSTOC.

FALLOPIAN TUBE CANCER

CHARACTERISTICS

- The origin of primary ovarian cancer, based on advancing genetic investigations and correlation with histopathologic evidence is most likely metastatic primary fallopian tube cancer (PFTC). Thus, fallopian tube, ovarian, and primary peritoneal cancers are now grouped under the same umbrella for diagnosis, treatment, and management as tubo-ovarian cancers. The incidence of PFTC was stated to be 0.41/100,000 women (119). Bilateral involvement is found in 5% to 30% of patients, and one third of patients have LN

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metastasis at the time of staging. Route of spread is transcoelomic, lymphatic, and hematogenous.

- Hu's criteria were established to assist in the definitive diagnosis of PFTC (120). This was further modified by Sedlis in 1978 (121) and the criteria are: a) the main tumor is in the tube and arises from the endosalpinx; b) the pattern histologically reproduces the epithelium of fallopian tube mucosa and shows a papillary pattern; c) the transition between benign and malignant tubal epithelium should be demonstrable; d) and the ovaries and endometrium are normal or contain less tumor than the tube.
- There is often a triad of symptoms: pelvic pain, a pelvic mass, and watery vaginal discharge (hydrops tubae profluens). This occurs in 11% of patients. A pelvic mass is diagnosed in 12% to 66% of patients.

PRE-TREATMENT WORKUP

- Workup includes a history and physical examination with lab tests. Tumor markers including a CA-125 are drawn. An abnormal Pap smear has been found to be positive in 18% to 60% of patients. Imaging with ultrasound, CT, or MRI can be helpful.

HISTOLOGY

- Ninety percent of tumors are serous, but other subtypes are found including endometrioid, transitional and mixed mesodermal Müllerian tumor.

STAGING

- Staging follows the same criteria as that for tubo-ovarian cancer.

TREATMENT

- Primary treatment is usually surgical to follow the general TOC protocols.
- Surgery includes full staging with a TH-BSO, LND (if less than stage IIIC), omentectomy, peritoneal biopsies, and debulking to microscopic residual disease.
- Chemotherapy follows the same principles as that of tubo-ovarian cancer with first-line platinum- and paclitaxel-based combination regimens.
- Treatment by stage and grade:
  - Stage I grade 1: definitive surgery
  - Stage I grade 2 or 3: surgery and adjuvant chemotherapy
  - Stage II to IV: surgery and (neo) adjuvant chemotherapy

SURVIVAL (Table 2.12)

Table 2.12 Fallopian Tube Cancer 5Y Survival by Stage

Stage	Relative 5Y survival (%)
I	87
II	86
III	52
IV	40

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SURVIVAL CARE

- Follows the same principles as that of TOC.

PRIMARY PERITONEAL CANCER

- Differentiation between primary peritoneal cancer (PPC) and primary tubo-ovarian carcinomas can be difficult. PPC may be unrecognized metastatic serous tubal intraepithelial carcinoma (STIC) or PFTC. Pathologic criteria previously established to determine a primary peritoneal site are: the bulk of tumor is on the peritoneum rather than on the ovaries; normal-sized ovaries are present or the ovaries are enlarged by a benign process; tumor involves the ovaries to a depth that is less than 5 mm and a width that is less than 5 mm; the tumor is serous by nature. Again, peritoneal, tubal, and ovarian cancers are now grouped under one heading for diagnosis, treatment, and management.
- PPC can be considered an expression of hereditary breast and ovarian cancer syndromes. There is a 2% to 4.3% risk of primary peritoneal cancer after prophylactic oophorectomy in hereditary cancer mutation carriers.
- Workup, staging, treatment, survival, and survival care follow the same principles as that of TOC.

GERM CELL TUMORS

CHARACTERISTICS

- GCTs are hypothesized to arise from an unfertilized ovum. They represent 15% to 20% of ovarian cancers, and 70% of ovarian tumors in women less than 30 years of age. The median age at diagnosis is 19 years, 30% are malignant, 60% to 75% are stage I at diagnosis, and 25% to 30% are stage III at diagnosis.
- Clinical symptoms include a mass, abdominal distension, bloating, pelvic pressure, or pain. Pain can occur from mass effect, torsion, and/or hemorrhage.
- Paraneoplastic syndromes are common: hyperthyroidism can occur from teratomatous thyroid tissue, hypertension from renin-producing teratomas, hypoglycemia from insulin production, as well as autoimmune hemolytic anemia from teratomas.
- 5Y survival (Table 2.13)

Table 2.13 Germ Cell Ovarian Cancer 5Y Survival by Stage

Stage	Relative 5Y survival (%)
I	98
II	94
III	87
IV	69

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PRE-TREATMENT WORKUP

- The pre-treatment workup includes a physical examination, CXR, abdominal pelvic imaging to include pelvic ultrasound, CT, or MRI, serum tumor markers, and a karyotype in short or premenarchal females.
- Serum tumor markers specific to histology include:
  - Dysgerminoma: human chorionic gonadotropin (hCG) (5%), lactate dehydrogenase (LDH)
  - Endodermal sinus tumor: alpha fetoprotein (AFP), LDH
  - Immature teratoma (IT): AFP, LDH
  - Embryonal carcinoma: hCG, AFP, LDH
  - Choriocarcinoma: hCG
  - Polyembryoma: hCG, AFP, LDH
  - Mixed: hCG, AFP, LDH

STAGING

- Staging for GCT is per tubo-ovarian cancer FIGO and AJCC protocols.
- Inadequately staged patients can be managed in two ways: with surgical re-exploration and staging; or chemotherapy without re-exploration, especially if the histologic subtype demands chemotherapy regardless of stage.

TREATMENT

- Surgical exploration is advised if a mass greater than 2 cm is found in premenarchal girls, or a mass greater than 6 to 8 cm is found in adolescents or postmenopausal females. If tumor markers such as AFP or hCG are found elevated, and pregnancy is ruled out, exploration should also be considered. Surgical treatment includes: washings, a USO if fertility is desired, along with staging biopsies, omentectomy, LND, and debulking of disease. If fertility is not desired, a hysterectomy with BSO is indicated in addition to the preceding staging procedures.
- The role of optimal cytoreduction is also important with these tumors. In a study of 76 patients, a 28% recurrence rate was seen if they were completely resected, versus a 68% recurrence rate if there was residual disease (122). In another study of patients treated with cisplatin–vinblastine–bleomycin (PVB), those with measurable disease had a 34% DFS versus 65% if optimally debulked (123).
- Adjuvant chemotherapy is recommended for all tumors except for stage IA dysgerminomas and stage IAG1 ITs. Chemotherapy is recommended to be platinum based and consists of bleomycin–etoposide–cisplatin (BEP) for three to four cycles. Total bleomycin dose should be evaluated to ensure it does not surpass 450 mg/m2, which is the toxicity level.
- The number of BEP cycles is debated. Three cycles are recommended for optimally debulked stages I to III disease. Four cycles are given for suboptimally debulked disease or stage IV disease. If tumor markers are still elevated, chemotherapy should continue for two cycles past normalization of these markers.

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RECURRENCE

- Recurrence is documented by physical examination, a rise in serum tumor markers, or imaging. 90% of relapses occur within 2 years.
- GCTs are classified as platinum resistant if there is recurrence within 4 to 6 weeks. Patients with elevated tumor markers at presentation and who do not achieve a negative marker status at four cycles are considered to be failure of response. Salvage chemotherapy should be implemented.
- Some clinicians have recommended salvage cytoreduction showing a 61% 5 YS if optimally salvaged versus 14% 5 YS in those not secondarily optimally cytoreduced (124).

FOLLOW-UP

- For nondysgerminomatous tumors, follow-up should occur every 3 months for the first 2 years, every 6 months up to 5 years.
- For dysgerminomas, a 10Y follow-up is recommended. Serum hCG and AFP should be measured for all patients, even if not initially elevated. 10–20% of tumors do relapse.

HISTOLOGIC SUBTYPES AND DIRECTED THERAPIES

- **Dysgerminomas** represent 40% of GCT; 95% are found in stage I. There is greater malignant potential if the tumor is larger than 10 cm, there is an elevated LDH, a high mitotic index, and necrosis. Five percent of tumors produce hCG and placental alkaline phosphatase (PLAP), due to the presence of syncytiotrophoblastic tissue.
  - Adjuvant therapy is indicated for patients staged IB or greater. BEP for three to four cycles is the recommended regimen; alternatively radiation therapy (XRT) can be considered.
  - It is important to check a karyotype because 15% of patients are intersex with XY gonadal dysgenesis. If this is found, a prophylactic bilateral gonadectomy should be considered because of the high risk for contralateral dysgerminoma. Gonadectomy should be performed before puberty except in females with testicular feminization. The gonads should be removed after puberty in these cases.
  - If a dysgerminoma is found incidentally after primary surgery, restaging can be considered but is not always indicated, if there is no bulky disease.
  - For Stage IA patients, there is a 20% recurrence rate. If patients were unstaged, consider surveillance, and salvage therapies initiated at recurrence. If there is recurrent disease, XRT or chemotherapy can be administered.
- Gonadoblastomas are rare benign GCTs. These tumors have up to a 10% chance of malignant transformation. The gonads should be removed if a gonadoblastoma is found in a dysgenic gonad.
- Endodermal sinus tumors represent 22% of GCT.
  - The histologic pearl is the presence of Schiller–Duval bodies. These are hyaline bodies that resemble the glomerulus in the kidney.
  - All patients require adjuvant postoperative chemotherapy, which should begin within 7 to 10 days of surgery due to rapid growth of disease.

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Recommended therapy is BEP for three to four cycles, or POMB-ACE every 3 weeks for four cycles. Survival is 2% to 10% without chemotherapy. This is the most virulent of the GCT.

- Embryonal carcinoma is a rare tumor that occurs in younger patients. There are no trophoblastic tissues in this tumor. Adjuvant treatment should consist of BEP chemotherapy regardless of stage.
- Choriocarcinoma is a rare tumor, especially the nongestational type. Adjuvant treatment should consist of BEP chemotherapy regardless of stage.
- Polyembryoma is an extremely rare GCT with fewer than 40 cases reported in the literature. Embryoid bodies are seen at pathology. Adjuvant treatment consists of BEP chemotherapy regardless of stage.
- Mixed GCT constitutes 1% to 15% of all GCT. They most commonly consist of dysgerminomatous and endodermal sinus tumor components. Adjuvant treatment should consist of BEP chemotherapy regardless of stage.
- Mature cystic teratoma, also known as a dermoid, represents 95% of ovarian teratomas. All three germ cell layers are represented. This tumor does not constitute a malignancy. It can present as a mass, and it can cause pain via torsion or rupture (Figure 2.7).
  - The tubercle of Rokitansky is a mural density seen on radiologic imaging.
  - Treatment is surgical with a cystectomy or USO.
  - Malignant degeneration can occur in 1% to 2% of mature cystic teratoma (MCTs). This is usually found in a focus of squamous cell carcinoma from skin lining the cyst. Intraoperative spill of sebaceous contents can cause a chemical peritonitis.
  - Gliomatosis peritonei is the presence of benign peritoneal implants of mature neuroglia. These implants usually undergo remission upon resection of the primary tumor.
- **Immature teratomas** constitute 20% of GCTs. An immature teratoma (IT) is defined as the presence of any immature neural tissue. Immature neural tissue is seen as rosettes or neurotubules within the tumor.

Figure 2.7 Dermoid tumor with teeth.

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- The amount of immature tissue on one low-power slide determines the grade. The grading system for IT is: grade (G) 1, 1 low-power field (LPF 10×) of neural elements in any slide; G2, no greater than a total of 3 LPFs of neural elements in any slide; G3, greater than 3 LPFs full of neural elements in at least one slide.
- Chemotherapy is indicated for all patients except stage IA grade 1. Recommended therapy is BEP every 3 weeks for three to four cycles.
- A second-look laparotomy is recommended if there is residual tumor seen on imaging after completion of chemotherapy. This can remove chemoresistant disease or determine if there was conversion to mature teratoma.

GCT TRIALS

- GOG 10: 76 patients with malignant GCTs received vincristine, dactinomycin, and cyclophosphamide (VAC) postoperatively; 54 patients were optimally debulked; 28% of these failed compared to 68% of those who were incompletely resected and failed. Therefore, PVB was trialed for those who were suboptimally resected (122).
- GOG 45: 97 eligible patients with stage II to IV or recurrent disease were treated with three to four cycles of PVB. Of 35 patients with tumors other than dysgerminoma who had clinically measurable disease, 43% had a CR. The OS was 71% and the DFS was 51% (123).
- GOG 78: this study evaluated 93 eligible patients with surgically staged and resected GCTs. Three cycles of BEP were given as primary adjuvant therapy; 89 of the 93 patients were continuously disease free. At second-look laparotomy, two patients were found to have foci of IT but remained CCR. Final conclusions were that 91 of 93 patients were progression free after surgery and three cycles of BEP. Patients with IT may benefit from secondary debulking if residual disease is identified (125).
- GOG 90: 20 patients with incompletely resected ovarian dysgerminoma were treated with cisplatin, bleomycin, and either vinblastine or etoposide. Consolidation chemotherapy with VAC was included for some. 11 patients had clinically measurable disease postoperatively, and 10 responded completely. Fourteen second-look procedures were done, and all were negative; 19 of 20 patients were disease-free with a median follow-up of 26 months (126).
- GOG 116: this study evaluated 39 eligible stage IB to III completely resected dysgerminoma patients. Carboplatin 400 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1,2,3 q28 days for three courses were used as primary adjuvant therapy. This doublet therapy was found to be well tolerated for those who needed to reduce chemotoxicity. There were no recurrences. Critics suggest the lack of bleomycin can contribute to an inferior outcome such as that seen in testes cancer (pharmacologic sanctuary), so the doublet should not be used without bleomycin in ovarian GCTs (127).
- A GOG assessment of SLL in GCT evaluated 117 patients from GOG studies 45, 78, and 90. Of the 45 patients treated with BEP after optimal debulking, 38 had a negative SLL. They concluded there was no need for SLL. A subgroup analysis suggested that SLL may be of value in approximately 33% of patients with suboptimal debulking for GCT with teratomatous elements. Of the 24 patients with teratoma in the primary tumor, 16 patients had bulky residual disease; 14 of 16 patients were disease free after secondary debulking (135).

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SEX CORD STROMAL TUMORS

CHARACTERISTICS

- Sex cord stromal tumors represent 5% to 8% ovarian malignancies and 5% of childhood tumors. They are bilateral in 2% of patients. 85% of these tumors produce steroid hormones. The route of spread is transcoelomic, lymphatic, and hematogenous.
- 5Y survival (Table 2.14)

Table 2.14 Sex Cord Stromal Ovarian Cancer 5Y Survival by Stage

Stage	5Y survival (%)
I	95
II	78
III	65
IV	35

PRE-TREATMENT WORKUP

- The pre-treatment workup includes serum hormonal evaluation (free testosterone, estradiol, 17-hydroxy-progesterone, serum cortisol, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), AFP, LDH, inhibin A, inhibin B, and hCG), and imaging including CXR and ultrasound, CT, or MRI.

STAGING

- Staging is the same as TOC. There are data to suggest a primary LND does not often yield positive results (128).

TREATMENT

- Surgical treatment is with washings, a USO if fertility is desired, along with staging biopsies, omentectomy, LND, and debulking of disease. A D&C should be considered if fertility preservation is undertaken especially for granulosa cell tumors. If fertility is not desired, a hysterectomy with BSO is indicated.

HISTOLOGY (Table 2.15)

Table 2.15 Ovarian Stromal Tumor WHO Classification Overview and Risk of Malignancy

Granulosa cell tumors	
Adult	Malignant
Juvenile	Malignant
Thecoma	
Thecomas, typical	Benign

(*continued*)

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Table 2.15 Ovarian Stromal Tumor WHO Classification Overview and Risk of Malignancy (*continued*)

Thecomas, luteinized	Malignant potential
Thecoma with increased mitotic figures	Malignant potential
Fibroma	
Cellular fibroma	Malignant potential
Cellular fibroma with increased mitotic figures	Malignant potential
Fibrosarcoma	Malignant
Stromal tumor with minor sex cord elements	Benign
Sclerosing stromal tumor	Benign
Signet ring stromal tumors	Benign
Unclassified	Malignant potential
Sertoli–Leydig cell tumors	
Well differentiated	Malignant potential
Intermediate differentiation	Malignant
Poorly differentiated	Malignant
Sertoli–Leydig tumors with heterologous elements	Malignant
Sertoli cell tumors	Malignant potential
Leydig cell tumors	Benign
Stromal–Leydig cell tumors	Benign
Sex cord tumors with annular tubules (SCTAT)	Malignant
Microscopic SCTAT associated with Peutz–Jeghers syndrome	Benign
Gynandroblastoma	Malignant/malignant potential
Unclassified sex cord stromal tumors	Malignant potential
Steroid cell tumors	Malignant

Source: Ref. (129). Tavassoeli FA, Devilee P, eds. *WHO Classification of Tumours, Pathology and Genetics: Tumours of the Breast and Female Genital Organs*. Lyon: IARC; 2003.

- **Stromal tumors**
  - **Granulosa cell tumors**
    - Granulosa cell tumors represent 1% to 2% of ovarian tumors.
    - These tumors tend to produce high levels of estrogen that can cause the refeminization of postmenopausal patients, and isosexual precious puberty in prepubertal girls. Patients may experience associated vaginal

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bleeding, with up to 50% of patients having endometrial hyperplasia and up to 5% with a concordant uterine cancer.
- The histologic pearls are: the presence of Call–Exner bodies and coffee bean nuclei.
- Most granulosa tumors are of the adult type (95%) and the rest are of the juvenile type.
- The juvenile type is relatively benign in early stages but can be aggressive in advanced stages. Associated syndromes are Ollier's disease (enchondromatosis) and Maffucci's syndrome (hemangiomas and sarcomas). The OS for stage I juvenile tumors is 97% versus 23% for stage III/IV. There are no Call–Exner bodies in the juvenile type.
- It is important to check a serum estradiol (>30 pg/mL in a postmenopausal woman is abnormal) and both the alpha and beta inhibin levels.
- Treatment is surgical with comprehensive staging.
- Adjuvant chemotherapy is considered for stage IC and higher. Recurrence is often indolent at 5 to 20 years. See MITO-9 study.
- Prognostic factors for adverse outcomes are: size greater than 10 cm, rupture, greater than 2 mitosis/10 HPF, LVSI, and nuclear atypia.
- For recurrent or metastatic disease, patients can be retreated with BEP or other regimens to possibly include platinum with paclitaxel, high-dose progestins, gonadotropin-releasing hormone (GnRH) agonists, or XRT. One study demonstrated a 43% CCR with XRT in patients with measurable disease (130). Another study has shown an 86% RR for granulosa cell tumors treated with XRT (131).

- **Thecomas**
  - Thecomas represent 1% of ovarian tumors and are bilateral in 3%. They are benign tumors. They can produce estrogen.
- **Fibroma–fibrosarcoma**
  - Fibromas are the most common sex cord stromal tumor and 10% are bilateral. They are benign tumors. They occasionally secrete estrogen. They have an association with Meigs syndrome, which is the presence of an adnexal fibroma, ascites, and a pleural effusion.
- **Sex-cord Tumors Androblastomas**
  - This tumor is diagnosed at a median age of 30 years. This tumor can cause virilization. It is important to follow the serum AFP and testosterone. Adjuvant chemotherapy is recommended if the tumor contains heterologous elements or is poorly differentiated. Recurrence is usually within the first 2 years.
- **Sertoli cell tumor**
  - Sertoli cell tumor is also called a Pick's adenoma.
  - It produces estrogen in 65% of patients and can also produce androgens. It rarely produces hyperaldosteronism with associated hyperkalemia and hypertension.
  - The histologic pearl is: the Pick's body.
  - There is an increased risk of malignancy if: hemorrhage, necrosis, a high mitotic count, or poor differentiation is present.

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- **Leydig cell tumors**
  - Leydig cell tumors produce androgens in 80% and estrogen in 10% of patients; 2.5% are malignant. They usually present after the age of 50 years and are associated with thyroid disease.
- **Sertoli–Leydig cell tumor**
  - Sertoli–Leydig cell tumors can cause virilization in 1/2 to 2/3's of patients. Most tumors produce testosterone and this can cause menstrual irregularities.
  - The histologic pearl is: the crystals of Reinke.
  - Ninety percent are found at stage I, and less than 20% are malignant.
  - For those who are malignant: 10% are grade 2 and 60% are grade 3. Malignant tumors tend to have more necrosis, are larger, and hemorrhage more frequently.
  - Adjuvant chemotherapy should consist of BEP if malignant.

- **Gynandroblastoma**
  - Gynandroblastoma tumors can produce androgens and estrogens. These tumors can have both granulosa and Sertoli–Leydig components.
- **Sex cord tumor with annular tubules**
  - Sex cord tumors with annular tubules can produce estrogen. Two thirds are bilateral.
    - These tumors can be associated with Peutz–Jeghers (PJ) syndrome and are benign when they have this association. PJ syndrome has an associated 15% risk of cervical adenocarcinoma (adenoma malignum) and hysterectomy should be considered after fertility is concluded.
    - If patients are not diagnosed with PJ syndrome, these tumors are considered malignant. Treatment for non-PJ syndrome patients is surgical with a USO, LND, and staging. A D&C, endocervical curettage (ECC), and colposcopy should be performed if fertility is desired, and a TH-BSO otherwise.
- **Unclassified**
  - **Lipid cell tumors**
    - Lipid cell tumors can be virilizing and produce Cushing's syndrome. They produce estrogen, progesterone, and testosterone.
    - These are malignant in 20% of cases. Indications of malignancy are: pleomorphism, necrosis, a high mitotic count, and a size greater than 8 cm.
    - Adjuvant BEP chemotherapy is recommended if found to be malignant.
  - **Sex cord tumors not otherwise specified**
    - Sex cord tumors not otherwise specified produce a variety of hormones; up to 17% of patients have Cushing's disease.
    - Forty-three percent of these tumors are malignant. Malignant tumors contain fibrothecomatous areas and/or granulosa cell-like proliferation as well as areas of tubular differentiation.
    - Adjuvant BEP chemotherapy is recommended if malignant.

5Y SURVIVAL

- Dysgerminoma
  - Stage I: 90% to 95%
  - All stages: 60% to 90%

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- Endodermal sinus tumor
  - Stage I and II: 90%
  - Stage III and IV: 50%
- Immature teratoma
  - Stage I: 90% to 95%
  - All stages: 70% to 80%
  - Grade 1: 82%
  - Grade 2: 62%
  - Grade 3: 30%
- Embryonal carcinoma
  - All stages: 39%
- Choriocarcinoma: poor
- Polyembryoma: poor
- Mixed: depends on tumor composition
- Granulosa cell:
  - Stages I, II: 85% to 95%
  - Stages III, IV: 55% to 60%
- Sertoli–Leydig:
  - Grade 3: poor survival

SEX CORD STROMAL TUMOR TRIALS

- GOG 115: this study evaluated 57 eligible patients who had incompletely resected stages II to IV ovarian stromal malignancies. BEP was used as first-line therapy every 3 weeks for four cycles. The endpoint was negative second-look laparotomy: 37% had negative findings. Patients with measurable disease had the highest risk of progression and death. BEP was found to be active in stromal tumors (132).
- GOG 264: a randomized phase II trial of paclitaxel and carboplatin versus bleomycin etoposide and cisplatin for newly diagnosed advanced stage and recurrent chemo-naive sex cord stromal tumors of the ovary. Results pending with estimated completion date 2024.
- MITO-9: 40 patients with stage 1C granulosa cell tumor were retrospectively reviewed. 35% had fertility-sparing treatment, 22.5% received adjuvant BEP or carboplatin/taxol, 35% relapsed, and there was no difference in DFS between those who received and those who did not receive adjuvant chemotherapy. 5Y DFS was 27% compared to 50%, $p = 0.4$. Adjuvant chemotherapy was not predictive for recurrence although incomplete surgical staging was. This study was limited by being a retrospective review and by low power (133).
- Surveillance options after initial surgery for pediatric and adolescent girls with stage I ovarian GCTs are debatable. High-risk histologies or stage IB and higher should be, in our opinion, considered for adjuvant chemotherapy.
  - A report from the Children's Oncology Group states that some girls can be watched rather than treated upfront due to high salvage rates. Careful discussion should be held with patient and family due to this being a small study 48% recurrent with surveillence, and one death was observed. 25 girls were reviewed with a median age of 12 years. Of these, 23 patients

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had an elevated AFP at diagnosis. The predominant histology was YST, with embryonal, or choriocarcinoma also represented. The median follow-up was 42 months. Surveillance was: measurement of serum tumor markers and radiologic imaging at defined intervals, AFP and b-HCG every 3 weeks through week 9, monthly from 2 to 6 months, and every 3 months from 6 to 24 months. LND was not required, sparing of fallopian tubes was allowed, and no staging biopsies were needed. In those with residual or recurrent disease, a compressed BEP regimen was initiated every 3 weeks for three cycles. 12 patients had evidence of persistent or recurrent disease. The 4Y event free survival (EFS) was 52%, the median time to recurrence was 2 months. All patients had elevated AFP at recurrence. 11 of 12 patients received successful salvage chemotherapy with a 4Y OS of 96%. There was one death. The compressed regimen of BEP was: cisplatin 33 mg/m^2 on days 1 to 3, etoposide 167 mg/m^2 on days 1 to 3, bleomycin 15 mg/m^2 on day 1; for three cycles (134).

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Uterine Cancer

CHARACTERISTICS

- Uterine corpus cancer is the most common female gynecologic cancer in the United States with an estimated 61,380 cases and 10,920 deaths in the United States in 2017. Currently, endometrial adenocarcinoma is the most common malignancy of the female genital tract and ranks as the fourth most common cancer in females.
- **Risk factors** for endometrial cancer include the triad of obesity, diabetes, and hypertension. Other risk factors are a prolonged exposure to estrogens, nulliparity, early menarche, late menopause, and unopposed estrogen hormone therapy.
- Most women present with abnormal uterine bleeding. Of those postmenopausal women who do present with bleeding, 10% result in a diagnosis of uterine cancer.
- Other presenting signs and symptoms can be menorrhagia, intermenstrual bleeding, pain, pyometria, hematometria, and an abnormal Pap smear.
- Hyperplasia and cellular atypia, alone or combined, have known rates for progression to uterine cancer (Table 2.16) (1).
    - According to one collaborative study, a diagnosis of complex atypical hyperplasia was associated with a 43% chance of concurrent endometrial cancer. Of these specimens, 31% had myometrial invasion and 10% had greater than 50% myometrial invasion (2).

Table 2.16 Uterine Hyperplasia and Risk of Progression to Cancer

Type of hyperplasia	Total cases	Persisted (%)	Progressed (%)	Mean years follow-up
Simple	93	19	1	15.2
Complex	29	17	3	13.5
Atypical simple	23	23	8	11.4
Atypical complex	45	14	29	11.4

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PROGNOSTIC FACTORS

Stage is the most important prognostic factor. Other factors include depth of myometrial invasion (DOI), LVSI, grade, histology, tumor size, patient age, and hormone receptor status.

PRE-TREATMENT WORKUP

- Workup for abnormal bleeding begins with a history and physical examination. Evaluation involves endometrial biopsy (EMB) with endocervical curettage or D&C. Pelvic ultrasound and Pap smear may also be performed, but are insufficient modalities used alone for persistent abnormal bleeding.
- An endometrial stripe thickness that is 5 mm or greater in a postmenopausal patient is abnormal and biopsy should be performed. The accuracy of EMB and D&C are relatively the same, between 91% and 99%, when compared with final pathology (2).
- Women with the following should be ruled out for cancer via endometrial biopsy: postmenopausal women with bleeding; postmenopausal patients with pyometria; asymptomatic postmenopausal women with endometrial cells on Pap smear (especially if atypical); perimenopausal patients with intermenstrual bleeding or increasingly heavy periods; and premenopausal patients with abnormal uterine bleeding, particularly if there is a history of anovulation.
- In women over the age of 35 years with abnormal bleeding, an EMB should be performed. 25% of cancers occur in premenopausal women and 5% occur in women less than 40 years of age.
- The pre-treatment workup for uterine cancer includes a CXR and abdominal-pelvic imaging. This can be with a pelvic ultrasound, CT, or MRI. Lab tests include a CBC, comprehensive metabolic panel (CMP), and CA-125 (which can predict LN metastasis) (Figure 2.8).

Figure 2.8 Uterine cancer on CT.

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CATEGORICAL DIVISIONS

- **Histologic grouping:** epidemiological and clinical studies suggest that endometrial cancers be separated by histologic appearance and behavior into two groups: type I and II tumors. Genetic evaluation is moving toward categorizing tumors outside standard histological status into four separate categories.
  - Type I tumors are the most common. The main risk factor in type I carcinomas is hyperestrogenism. These tend to be hormonally responsive and have an 83% all stage 5Y survival. These cancers typically have a favorable prognosis with appropriate therapy (Figure 2.9).
    - The most common type I cancer is endometrioid adenocarcinoma, which occurs in 75% of cases.
    - Adenosquamous carcinoma is diagnosed in 18% to 25% of uterine cancers. The behavior is similar to that of endometrioid cancer.
    - Villoglandular carcinoma occurs in 6% of uterine cancers. This subtype is distinguished by delicate fibrovascular cores. It is usually of low grade and is more differentiated than endometrioid adenocarcinoma.
    - Secretory carcinoma occurs in 2% of uterine cancers and appears as a well-differentiated glandular pattern with intracytoplasmic vacuoles containing glycogen, similar to secretory endometrium. It is usually grade 1.
    - Mucinous carcinoma is diagnosed in 5% of cases and mucin is present as the major cellular component. There are columnar cells that are basally oriented or pseudostratified. It is necessary to rule out other cancers such as colon, mucinous ovarian, and primary endocervical cancers. It has the same prognosis as endometrioid cancer.
    - Squamous carcinoma is associated with cervical stenosis, pyometria, and chronic inflammation. It is important to rule out a primary cervical cancer origin. It has a poorer prognosis.
    - IHC to differentiate type I tumors from type II includes: estrogen receptor (ER)/progesterone receptor (PR)+, p53–, and WT-1 negative.

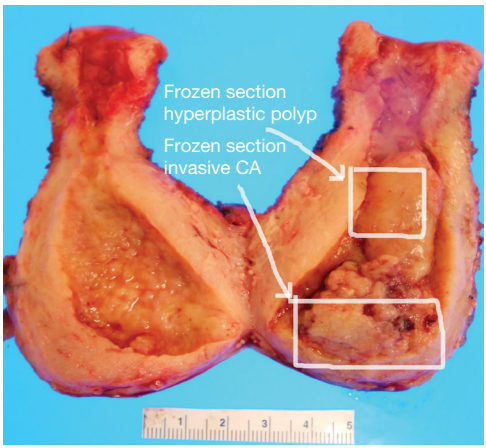

Figure 2.9 Endometrioid uterine cancer.

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- Type II cancers are poorly differentiated tumors, and are histologically represented by the serous, clear cell (CC) and malignant mixed Müllerian tumors (MMMT) histologies. Type II tumors are more biologically aggressive and have a 53% 5 YS for all stages. Type II tumors account for 15% of uterine carcinomas, but represent 50% of all relapses. These type II tumors are classified as high risk, high grade, and are unresponsive to hormonal therapy.
  - **Serous** uterine carcinoma is diagnosed in 10% to 15% of endometrial cancers. If there is 10% or less serous component, it is called a mixed tumor. This subtype resembles serous carcinoma of the ovary. It is often found at an advanced stage. The depth of invasion is often not predictive of LN metastasis, and extrauterine disease is found in 60% of tumors. If the cancer is identified in a polyp without other evidence of uterine disease, 38% of patients will be found to have extrauterine spread. Intraperitoneal spread is common even when myometrial invasion is minimal. When comprehensively staged, 70% of patients are found to have advanced-stage disease: 25% of apparent stage I cancers (3) have omental metastasis and 25% of patients have upper abdominal disease (4). Microscopically, there are fibrous papillary fronds, picket fencing of the terminal cells, LVSI is common, and psammoma bodies are often present. It is high grade by definition. There is a 2% rate of *BRCA1* mutations in uterine serous cancer patients. Nine percent of women with a history of breast cancer followed by uterine serous cancer have a *BRCA 1/2* mutation (5).
  - IHC for serous cancers: ER/PR variable, WT-1 negative, p53+.
  - Clear cell carcinoma is diagnosed in 5% of uterine cancers. It also is an aggressive tumor. The cells contain a large amount of glycogen and when processed for histology, the glycogen in the cells gives an appearance of cellular clearing and nuclear hobnailing.
  - Mixed Müllerian mesodermal tumors (MMMT; carcinosarcoma) are now thought to be metaplastic epithelial (or carcinomatous) cancers. These tumors tend to occur in older women with a median age of 65 to 75 years. Other characteristics include obesity, nulliparity, and diabetes. Tumor can be seen via speculum examination in 50% of women. Pathologically, there is a mixture of carcinomatous and sarcomatous tissues. The carcinomatous component is most commonly endometrioid, but can be of serous or CC histology. Prognosis is mainly dependent on the epithelioid histology. The sarcomatous/nonepithelial component is commonly an endometrial stromal sarcoma (ESS), but can be leiomyosarcoma (LMS), rhabdosarcoma, or chondrosarcoma. The presence or absence of heterologous elements is not predictive of outcome. Studies have shown similar allelic losses present in both the carcinomatous and sarcomatous areas of MMMTs in multiple patients. This suggests a late divergence in phenotype and a common abnormal clone for the entire cancer. Prior tamoxifen use has been implicated in this tumor's development. The median time of exposure to diagnosis of MMMT was 9 years and ranges to a relative risk (RR) of 15.9 (6). Prior pelvic XRT has also been noted to have a causal effect: in 23 patients with prior pelvic XRT,

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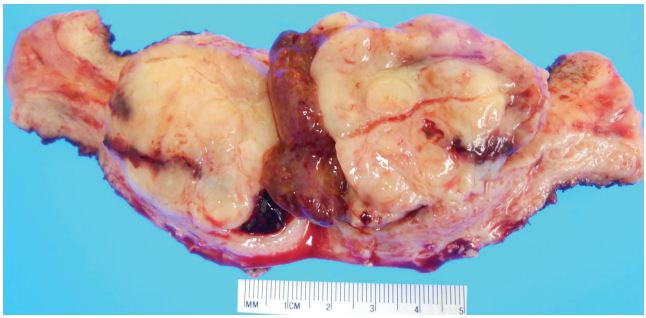

Figure 2.10 Mixed Müllerian mesodermal tumor (MMMT) uterine cancer.

35% had an MMMT uterine cancer. Surgical management is critical for staging and optimization of treatment. 20% of patients with clinical stage I and II are upstaged by LND. Cytoreduction in advanced stage disease (III and IV) with optimal resection was associated with improved survival of 52.3 months versus 8.6 months ($p < 0.0001$), with another study showing similar results in debulking to no residual versus optimal (less than 1 cm) and suboptimal disease with a PFS of 0.8 versus 8.6 versus 13 months and OS of 4.5 versus 12.7 versus 29.6 months, respectively (Figure 2.10) (7).

- **Genetic groupings:** adjuvant recommendations may be determined by genetic grouping in the future (8).
  - POL-E: ultramutated
  - Copy number high: serous/CC/some G3 adenocarcinomas
  - Copy number low: commonly G1/2 endometrioid adenocarcinomas
  - Microsatellite instability (MSI): genomic, somatic, and epigenetic (hypermethlyated)

STAGING

- Staging is **surgical**. In 1988, the staging was changed from clinical to surgical. Surgical staging was further revised in 2009 (Table 2.17A–D).
- **Grade** is specified as a three-tiered system: grade 1 tumors are highly differentiated, with less than 5% of the tumor containing solid areas; grade 2 tumors are moderately differentiated with 6% to 50% solid areas; grade 3 tumors are poorly differentiated carcinomas with greater than 50% of the tumor containing solid components. If nuclear atypia is present at a higher degree than the stated histological grade, the overall grade is increased by one grade.

TREATMENT

- Treatment is primarily surgical staging to include: pelvic washings, hysterectomy, bilateral salpingo-oophorectomy, LND, omentectomy and peritoneal biopsies (especially for the type II tumors), and surgical debulking of extrauterine/metastatic disease.

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Table 2.17A AJCC 8th Edition: T Category		
T	**FIGO**	**T Criteria**
TX		Primary tumor cannot be assessed.
T0		No evidence of primary tumor.
T1	I	Tumor confined to the corpus uteri, including endocervical glandular involvement.
T1a	IA	Tumor limited to the endometrium or invading less than half the myometrium.
T1b	IB	Tumor invading one half or more of the myometrium.
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus.
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium.
T3a	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis).
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement.
T4	IVA	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4).

Table 2.17B N Category		
N	**FIGO**	**N Criteria**
NX		Regional LNs cannot be assessed
N0		No regional LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) not >0.2 mm
N1	IIIC1	Regional LN metastasis to pelvic LNs
N1mi	IIIC1	Regional LN metastasis (>0.2 mm but not >2.0 mm in diameter) to the pelvic nodes
N1a	IIIC1	Regional LN metastasis (>2.0 mm in diameter) to pelvic LNs
N2	IIIC	Regional LN metastasis to para-aortic LNs, with or without positive pelvic LNs
N2mi	IIIC2	Regional LN metastasis (>0.2 mm but not >2.0 mm in diameter) to the para-aortic LNs, with or without positive pelvic LNs
N2a	IIIC2	Regional LN metastasis (>2.0 mm in diameter) to para-aortic LNs, with or without positive pelvic LNs
LN, lymph node.		

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Table 2.17C M Category

M	FIGO	M Criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal LNs, intraperitoneal disease, lung, liver, or bone)

LN, lymph node.

Table 2.17D Stage Grouping

When T is	And N is	And M is	The stage group is
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	III
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1/N1mi/N1a	M0	IIIC1
T1-T3	N2/N2mi/N2a	M0	IIIC2
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

- Treatment approaches:
  - Laparotomy
  - Minimally invasive (preferred)
    - Laparoscopic assisted vaginal
    - Robotic assisted
- Treatment modifications:
  - Conversion to laparotomy from laparoscopy: in one study this occurred in 17.5% of patients with body mass index (BMI) of 25, 26.5% with a BMI 34 to 35, and 57% of patients with BMI greater than 40. Port site metastasis occurred in 1% (9).
  - The ability of infrarenal/PA-LND was 81% in one study when the BMI was greater than 35 kg/m^2, compared to 95% when the BMI was less than 35 (10).

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- Ovarian conservation in young women with uterine cancer: only 18% of women less than 45 years old have stage IAG1 disease. The risk of a synchronous ovarian malignancy can be as high as 19%–25% in younger women. Bilateral salpingo-oophorectomy (BSO) should be considered for all women with uterine cancer per Society of Gynecologic Oncology (SGO) guidelines. If ovarian conservation is desired, patients should be stage IA and G1-2. A retrospective review showed that conservation was not independently associated with survival (HR 0.94; 95% CI: 0.65–1.37) (11). Younger women have a higher risk of genetic mutations. The risk of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome and ovarian malignancy is up to 10% if women harbor this genetic mutation. MRI is the best mode to evaluate for DOI and cervical involvement when considering preoperative radiologic staging for possible ovarian preservation (12).
- Morcellation: the risk of a fibroid harboring a LMS is 0.3% to 0.49%. Regardless, morcellation is not recommended for uterine cancer cases to avoid tumor spill and spread, or alter pathologic evaluation. Alternatives to morcellation for laparoscopic approaches to surgery are minilaparotomy or morcellation within an endoscopic bag after vaginal delivery of the specimen (13).
- Sentinel LND: this strategy remains under investigation (category 3) and careful consideration should be given to not performing this procedure with type II tumors. If it is considered, surgeon experience, adherence to an sentinel LND algorithm or clinical study, and the use of pathologic "ultrastaging" are key factors for successful SLN mapping. Serous/CC/MMMT histologies should not undergo this type of LN assessment.

- **Lymph node dissection**
  - The boundaries for pelvic LND (P-LND) are the following: the distal half of the common iliac vessels, the anterior and medial aspect of the external iliac vessels, the ureter or (superior vesicle artery below the common iliacs) medially, the circumflex iliac vein distally, and the obturator nerve inferiorly. The PA-LN boundaries are the following: the fat pads over and lateral to the great vessels, the inferior mesenteric artery superiorly, and the mid common iliac vessels inferiorly. For a high PA dissection, the LNs up to the renal vessels are removed medial to the ureters and anterior to the great vessels.
  - There is much controversy to the benefit and/or extent of an LND. LND has been shown not to increase the duration of surgery significantly. Some practitioners perform an LND based on tumor risk factors. Others recommend a comprehensive LND for all surgical candidates. Others have provided data that show that a LND is not therapeutic but can provide staging information to guide adjuvant therapies.
  - For those providers who choose a selective LND, the **Mayo criteria** is often employed to determine if a patient is low risk for LN metastasis. The Mayo criteria are: grade 1 or 2 disease; necessarily tumor size that is 2 cm or less; and ≤50% myometrial invasion. If all these criteria are met, patients have a less than 5% chance of positive LNs (14). Frozen section should be employed for this decision analysis. The accuracy of frozen section decreases with

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grade: 87% accurate with grade 1, 65% with grade 2, only 31% with grade 3 (15). Doering et al correlated visual inspection for DOI with frozen section and found 91% accuracy (16), and Franchi et al supported this data with 85% accuracy and 72% sensitivity (17).

- For those who perform comprehensive LND, the following benefits are cited: there may be a therapeutic benefit with removal of micrometastasis; there is a 22% chance of extrauterine disease found with surgical staging; and 20% of tumors are upgraded at final pathology. Data have shown that removing nodes provides a survival benefit (18,19). An improvement in survival from 72% to 88% has been reported for patients undergoing lymphadenectomy with more than 11 LNs removed (20). Using Surveillance, Epidemiology, and End Results (SEER) data, Chan et al showed that in patients staged IB grade 3 and above, more than 20 LNs removed was found to provide the best OS (21). In low-risk patients, there was no association with LN count and survival. The PORTEC 1 trial subset of stage IC grade 3 (unstaged) patients who were treated with pelvic XRT had a 5 YS of only 58%. Most recurrences were distant (22). In contrast, stage IIIC patients staged and treated have a 5 YS of 57% to 72% (23,24).
- In some instances, LND is not performed. This can occur when cancer is found incidentally after hysterectomy. Postoperative pathological review can risk stratify patients for possible post hoc staging. There can be intraoperative complications that prevent full staging, or the patient may be medically intolerant of the procedure. Body habitus may also prohibit adequate staging: in the Lap-2 data, 50% of patients with a BMI greater than 40 were not able to have a para-aortic (PA-LND) performed (9). For those who support no LND, data from the following two randomized studies are commonly used.
  - The Bendetti Panici study evaluated 514 eligible clinical stage I uterine cancer patients. Patients were randomly assigned to systematic P-LND versus no LND. Researchers found that early and late postoperative complications were higher in the systematic LND group. LND improved staging as more patients were found to have advanced stage disease with LN involvement. (13.3% vs. 3.2%). However, the 5 Y DFS and OS were similar (81% vs. 85.9% in the lymphadenectomy arm and 81.7% vs. 90% in the nonlymphadenectomy arm) (25).
  - The ASTEC A Study in the Treatment of Endometrial Cancer, study (26, 27) evaluated 1,408 women with clinical stage I endometrial cancer and randomized them to standard surgery (hysterectomy, BSO, washings with PA LN palpation) or standard surgery plus lymphadenectomy. The primary outcome for this study was OS. The HR for death was higher in those who underwent comprehensive staging with LND, 1.16 ($p = 0.3$; 95% CI: 0.87–1.54). The absolute difference in 5Y OS was 1%.
  - Based on a surgical/pathological review, in patients thought to have disease confined to the uterus, extrauterine disease has been found in 22% of patients, LN metastasis has been found to occur in 9% to 13% of patients, and isolated para-aortic LNs have been found in 2% of patients. The rate of positive PA LNs is approximately half the rate of positive pelvic LNs (Figure 2.11). For those who were identified with positive PA LNs, 47 of

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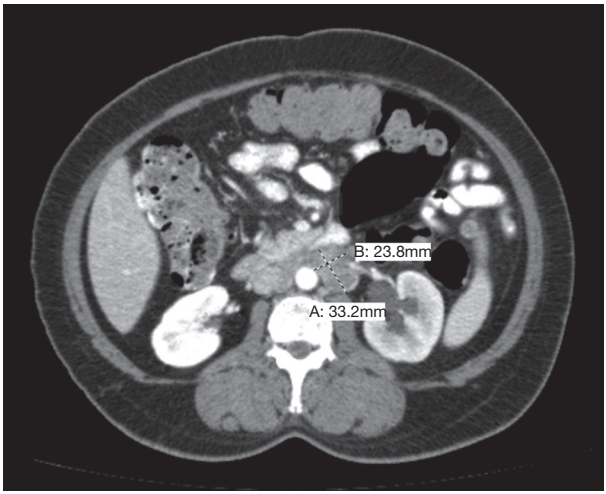

Figure 2.11 Uterine cancer on CT with para-aortic lymphadenopathy.

48 patients had one or more of the following: grossly positive pelvic LN; grossly positive adnexal metastasis; or outer one-third myometrial invasion (28). Omental metastasis has been found in up to 8% of patients (Table 2.18).

- If gross cervical involvement is seen at diagnosis: cervical biopsy and pelvic MRI should be performed for confirmation. If negative, TH-BSO and staging can be considered. If cervical biopsy is positive, a radical hysterectomy with BSO and surgical staging as primary treatment should be performed. Preoperative XRT consisting of external beam radiation therapy (EBXRT) and brachytherapy to a total dose of 75 to 80 Gy to point A can be alternative management. An adjuvant simple hysterectomy can then be considered. If not a surgical candidate, EBXRT and brachytherapy with consideration of systemic chemotherapy should be implemented. Reevaluation at a later date for surgical therapy should be performed. Systemic chemotherapy can also be an option alone for surgically inoperable patients.
- There are data to suggest that performing a radical hysterectomy, based on a positive endocervical curettage only, commonly shows no evidence of cancer on final pathology and may be overtreatment (29).
- If gross parametrial involvement is identified by physical examination or preoperative imaging, primary XRT with dosing analogous to that for cervical cancer (75–80 Gy) can be considered, followed by a simple hysterectomy, with or without chemotherapy.
- There are data to suggest that the incidence of omental metastasis is 6% to 8% and is associated with: grade of disease, extrauterine involvement, LN metastasis, deep myometrial invasion, and positive cytology.
- If there is **extrauterine disease** confirmed at presentation, neoadjuvant chemotherapy can be considered but most patients should proceed with

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Table 2.18 GOG 33 Risk Factors for LN Metastasis

Risk factor	Pelvic*	Para-aortic
Grade		
1	3	2
2	9	5
3	18	11
Depth of myometrial invasion		
Superficial	5	3
Middle	6	1
Deep	25	17
Site of disease		
Fundus	8	4
Cervix	16	14
Lymphovascular space invasion		
Negative	7	9
Positive	27	19

*percentage who developed nodal metastasis

LN, lymph node.

total hysterectomy, BSO, and surgical staging and debulking. If tumor appears to be surgically unresectable at presentation, EBXRT with/without brachytherapy and consideration of chemotherapy should be offered. Systemic therapy alone is another option. If liver metastasis is present and biopsy confirmed, systemic therapy with or without EBXRT and/or hormonal therapy can be considered. Palliative TH-BSO can be considered.

- If cancer is found incidentally on post hysterectomy specimen and:
  - Stage IA G1-2, less than 50% DOI, no LVSI, and the tumor size is less than 2 cm, observation is recommended.
  - If stage IA G3, greater than 1/2 DOI, LVSI, or the tumor size is greater than 2 cm, stage 1B, or stage II, surgical staging should be considered. Imaging can also be considered and if negative, with other low risk features, protocols for adjuvant XRT can be considered.
- **Adjuvant treatment** is commonly recommended in patients with endometrial cancer. Treatment is based on stage and pathologic risk factors. Early stage disease is defined as stages I and II. Advanced stage is defined as stages III and IV.
  - High intermediate risk (HIR) early stage disease is often treated with adjuvant XRT. HIR is classified by two different studies.
    - PORTEC 1: stratified patients into an intermediate high-risk subgroup for which treatment was recommended: patient age older than 60 years, DOI greater than half myometrial thickness, or grade 2 or 3 tumor.
    - GOG 99 stratified patients by age and risk factors. If a patient fell into any of the following groups, they were considered HIR: patients age ≥70 years

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with one risk factor, age 50 to 69 years with two risk factors, and any age with all three. The risk factors are: outer one-third myometrial invasion, grade 2 or 3 tumor, and LVSI.

- Absent RF:
  - Stage IA G1,2,3: can be observed or vaginal brachytherapy can be recommended
  - Stage IB G1,2,3: can be observed but more commonly vaginal brachytherapy with/without whole pelvic (WP) EBXRT (especially for G3) is recommended
- RF present:
  - Stage IA G1-2: observation or brachytherapy can be offered
  - Stage IAG3: brachytherapy, WP EBXRT, or observation can be offered
  - Stage IBG1-2: brachytherapy, WP EBXRT, or observation can be offered
  - Stage IBG3: brachytherapy with/without WP EBXRT with/without chemotherapy can be recommended

- High-risk early stage disease is defined variably. Stage I serous, CC, MMMT, and variably grade 3 endometrioid cancers put patients into the high-risk early stage disease category. There are data to show that (FIGO 1988) stage 1CG3 type I tumors had a 58% 5 YS. Some clinicians recommend chemotherapy and XRT for these high-risk patients. Stage IA type II tumors are recommended to have adjuvant therapy: preferably a combination of XRT and chemotherapy (three cycles of chemotherapy with brachytherapy). Stage IB cancers are recommended to have chemotherapy (three to six cycles) with/without vaginal XRT and/or EBXRT.
- Stage II disease: adjuvant XRT is recommended and cumulative data supports both WP EBXRT and brachytherapy treatment. Chemotherapy should be considered if a type II cancer is present and variably for G3 endometrioid cancer.
- Advanced-stage endometrial cancer. For advanced-stage disease (stages III/IV) treatment is primarily surgical with comprehensive staging and cytoreduction to microscopic status if possible. Adjuvant therapy is commonly multimodal including both XRT and chemotherapy, and can include hormonal therapies.
  - Stage IIIA: chemotherapy, EBXRT and/or brachytherapy, or both is recommended.
  - Stage IIIB: chemotherapy and/or EBXRT, and brachytherapy.
  - Stage IIIC: chemotherapy and/or EBXRT and/or brachytherapy
  - Stage IV: chemotherapy with/without EBXRT and/or brachytherapy.
  - There is literature to support cytoreduction in advanced metastatic uterine cancer.
    - Greer treated 31 patients with stage IVB disease with whole abdominal XRT. Those with residual disease less than 2 cm had a corrected 5 YS of 80% and an absolute 5 YS of 63%, whereas there were no survivors in the group with residual greater than 2 cm (30).

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- Goff evaluated patients with stage IV disease. Those who were cytoreduced had a longer median survival of 18 months compared to an 8-month survival in those who were not able to be cytoreduced (31).
- Bristow reviewed 65 patients with stage IVB endometrial cancer who underwent cytoreduction. Optimal cytoreduction (residual tumor ≤1 cm in maximal diameter) was accomplished in 55%. The median survival rate of patients who underwent optimal surgery was 34 months versus 11 months for patients with greater than 1 cm residual disease. Furthermore, patients with microscopic residual tumor survived significantly longer (median survival 46 months) compared to patients optimally cytoreduced but with macroscopic disease (32).
- Shih also suggested optimal cytoreduction for stage IV uterine cancer patients. Median survival: the median PFS was 40.3 months for patients with microscopic disease, 11 months for patients with any residual disease, and 2.2 months for patients who did not have attempted cytoreduction. The median OS was 42.2 months for patients with microscopic disease, 19 months for patients with any residual disease, and 2.2 months for patients that did not have attempted cytoreduction (33).
- There are data to support that most stage IIIA patients (adnexal spread of primary uterine disease) are clonally related metastatic tumors from one primary uterine tumor demonstrated on genetic analysis (34).

- Type II cancers
  - Early stage type II cancers (serous or CC histology): there are data to support platinum-based chemotherapy in addition to XRT for patients staged IA or above. Stage IA patients with no residual cancer in the hysterectomy specimen had no recurrences whether they received adjuvant therapy or not. 77% of stage IB patients not treated with adjuvant chemotherapy recurred versus no recurrences in the treated group; 20% of stage (FIGO 1988) IC patients who received chemotherapy recurred versus 80% who did not. Recurrences tended to occur at the vaginal cuff in patients not treated with brachytherapy, thus brachytherapy in combination with chemotherapy was recommended for all patients staged IA (with residual) or higher (35).
  - Maximal cytoreduction for stage IV serous uterine cancer can offer an improvement in survival. Bristow showed that patients with optimal cytoreduction had a median survival of 26.2 months versus 9.6 months in patients with suboptimal surgery. Patients with microscopic residual tumor had a significantly longer median survival of 30.4 months versus those with 0.1 to 1 cm residual disease who had a median survival of 20.5 months. A 41-month versus a 34-month versus an 11-month OS was observed for those patients who were microscopically cytoreduced, optimally cytoreduced to less than 1 cm, or suboptimally cytoreduced, respectively (32).
  - MMMT (carcinosarcoma) used to be classified as a uterine sarcoma. Recent data have suggested an improvement in survival with surgical cytoreduction (36). An adjuvant XRT trial from the EORTC eval-

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uated a subset of carcinosarcoma patients and found a trend toward improvement in local control with whole-pelvic radiation therapy (WP-XRT), but there was no improvement in survival (37). Chemotherapy in combination with XRT has been shown to be effective in treatment of MMMTs. Ifosfamide and paclitaxel have been shown to produce a RR of 45% (38).

RECURRENCE

Recurrent disease can be broken into local recurrence or distant recurrence. Local recurrence is divided into vaginal and pelvic. A full metastatic workup should be performed with a physical examination; imaging of the chest, abdomen, and pelvis; lab tests for baseline organ function; and possibly PET imaging. Patients who were previously radiated in the pelvis tend to fail distantly at 70%, only 16% recur vaginally, and 14% recur in the pelvis. Patients without prior pelvic XRT tend to fail vaginally at 50%, 21% fail in the pelvis, and 30% distantly.

- If the recurrence is vaginal, XRT can be administered. Prior XRT does affect response. In the PORTEC 1 trial, data on relapsed patients showed a 5 YS of 65% if patients had no prior adjuvant XRT versus 19% if they had prior XRT. The treatment of recurrence is WP-XRT in combination with brachytherapy dosed to 75 to 80 Gy if no prior XRT. There are data to support surgical cytoreduction of vaginal lesions to less than 2 cm. This is associated with an improvement in OS to 43 months versus 10 months (39).
  - If no prior XRT to the site of recurrence, then surgical cytoreduction to <2 cm should occur if possible with/without intraoperative radiation therapy (IOXRT), or EBXRT and brachytherapy dosed at 75 to 80 Gy.
  - If prior XRT given:
    - And prior brachytherapy only, then EBXRT or surgical resection with/without IOXRT can be provided.
    - If prior EBXRT, surgical resection with/without IOXRT or hormonal therapy, or chemotherapy can be offered.
- For pelvic recurrence including pelvic LN involvement:
  - Surgical resection can be considered followed by tumor directed EBXRT with/without chemotherapy
  - EBXRT with/without chemotherapy
- For extrapelvic recurrences:
  - For isolated recurrence: surgical resection with/without XRT or ablative therapy can be considered.
  - If upper abdominal recurrence is resectable it should be surgically reduced, chemotherapy should follow, and consideration of EBXRT can be offered.
  - If not resectable and low grade, asymptomatic, or ER/PR positive, hormone therapy can be attempted and if progression, then systemic chemotherapy provided. If symptomatic, grade 2-3, or large volume disease, then chemotherapy with/without palliative XRT should be provided.
  - For widely metastatic disease: if low grade, asymptomatic, or ER/PR positive: hormone therapy can be attempted and if progression, then systemic

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chemotherapy. If symptomatic, grade 2/3, or large volume disease, then chemotherapy with/without palliative XRT should be provided.

- Different chemotherapy regimens have been used. CAP: cyclophosphamide (500 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (70 mg/m^2), given every 4 weeks; single-agent paclitaxel at 250 mg/m^2 as 24-hr infusion (has shown a 36% response rate); or a combination of paclitaxel (175 mg/m^2), carboplatin AUC 6, and has shown a 40% response rate with an 8% complete response (40).
- Hormonal therapies, specifically progestins, have also been used. Medroxyprogesterone acetate (MPA) at a dose of 200 mg/day had a better response rate than 1,000 mg/day in the GOG 81 study. The overall response rate was 25%, and there was a higher response in ER and PR positive patients. Megace has also been used at a dose of 80 to 160 mg twice daily with an 18% to 34% response rate (41). For those patients who are ER positive on immunohistochemistry, tamoxifen or an aromatase inhibitor can be considered. If the patient is *Her-2/neu* positive, herceptin was found to have a 13% response rate in a phase II trial (GOG 181B) (42).
- Targeted therapies:
  - Cediranib monotherapy at 30 mg PO daily for a 28-day cycle was evaluated in 48 patients with recurrent or persistent endometrial cancer. The median age was 65.5 years, 52% had prior XRT and 73% had one prior chemotherapy regimen. A PR was seen in 12.5%. Median PFS was 2.65 months and median OS was 12.5 months and was well tolerated (43).
  - HNPCC/MSI confirmed patients: Pertulimuzab has been shown to be an actionable mutation medication.

FERTILITY SPARING OPTIONS (SEE ALSO CHAPTER 6)

- If the patient has fertility concerns, workup should include CT of the abdomen/pelvis; MRI of the pelvis, and pathology should be expertly reviewed.
- For consideration of fertility preservation: metastatic disease must be absent on workup, preferably no DOI seen on MRI, no contraindications (such as PE) should exist to medical therapy or desired pregnancy, grade must be well differentiated (G1), histology should be endometrioid subtype, and patients should undergo counseling with a reproductive endocrinologist as well as full informed consent that medical management is not the standard of care.
- Treatment: continuous progestin-based therapy with megace, medroxyprogesterone, or levonorgestrel intrauterine device (IUD). Resampling of the uterus should occur with D&C/EMB every 3 to 6 months. If there is a complete response by 6 months, conception can be encouraged. Completion hysterectomy should be offered at the end of desired fertility. If cancer is still present at 6 to 9 months, hysterectomy with BSO and staging is recommended.

POSTOPERATIVE HORMONAL REPLACEMENT THERAPY

Postoperative hormonal replacement therapy, namely estrogen, has been studied for quality of life and risk of recurrence. GOG 137 (44) evaluated estrogen HRT

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given to women with a history of uterine cancer. There was no increased risk of recurrence identified (RR was 1.27 80% CI: 0.916-1.77—the CI crossed 1.0, thus careful consideration of outcomes should be applied).

SYNCHRONOUS OVARIAN NEOPLASM

Five percent to 10% of women with a uterine cancer may have a **synchronous ovarian neoplasm.** Up to 25% of women under 40 years old can have this concurrent diagnosis. Concordant endometrioid histology in both the uterus and ovary are present 45% to 86% of the time. There is concordant grade in 69% of patients. Empirical criteria favoring metastatic uterine cancer over a synchronous ovarian tumor are: multinodular ovarian involvement, deep myometrial invasion, LVSI, bilateral ovarian involvement, and visualization of intratubal transit. Surgical staging or adjuvant recommendations are based on the worst-case scenario; that is, if the ovarian tumor is grade 3 and the uterine tumor is grade 1, chemotherapy would commonly be recommended.

SURVIVAL

Table 2.19A Endometrioid Uterine Cancer 5 YS by Stage

Stage	5 YS Endometrioid (%)
1A	88
1B	75
II	69
IIIA	58
IIIB	50
IIIC	47
IVA	17
IVB	15

YS, year survival.

Source: Ref. (45). Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 International Federation of Gynecology and Obstetrics' staging system for uterine corpus cancer. *Obstet Gynecol*. 2010;116(5):1141-1149.

Table 2.19B Serous Uterine Cancer 5 YS by Stage

Stage	5 YS Serous uterine cancer (%)
I	50–80
II	50
III	20
IV	5–10

YS, year survival.

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Table 2.19C Carcinosarcoma Uterine Cancer 5 YS by Stage	
Stage	**5 YS Carcinosarcoma (%)**
I	70
II	45
III	30
IV	15
YS, year survival.	

FOLLOW-UP

- Every 3 months for the first 2 years
  Every 6 months for the next 3 years
  Then annual examinations thereafter
- Physical and pelvic examination should occur at each visit. Pap smears have not been found to increase the detection of recurrence, nor has annual chest x-ray. CA-125 can be drawn if it was initially elevated.

TAMOXIFEN AND UTERINE CANCER

Adjuvant treatment of pre- and postmenopausal women with hormone receptor positive **breast cancer** has been **tamoxifen**. There are known gynecologic side effects from this medication. Aromatase inhibitors have been evaluated as crossover or primary therapy in some women, replacing tamoxifen treatment. Gynecologic side effects of tamoxifen can be vaginal bleeding, growth of uterine polyps in 8% to 36% of women, endometrial hyperplasia in 2% to 20%, and endometrial cancer ranging from 0% to 8%. The overall risk of subsequent uterine corpus cancer was increased more than twofold (observed-to-expected ratio [O/E] 2.17; 95% CI: 1.95–2.41) relative to the general SEER population in one study. The RR was substantially higher for malignant mixed Müllerian tumors (O/E 4.62; O 34; 95% CI: 3.20–6.46) than for endometrial adenocarcinomas (O/E 2.07, O 306; 95% CI: 1.85–2.32), although the excess absolute risk was smaller—an additional 1.4 versus 8.4 cancers per 10,000 women per year, respectively.

Ultrasound diagnoses an endometrial stripe that is greater than 5 mm in 50% of patients on tamoxifen; but endometrial stripes up to 8 mm can be considered normal in these patients. A routine annual EMB is not recommended unless these women are symptomatic with abnormal or postmenopausal bleeding of significant atypical vaginal discharge (46).

NOTABLE STUDIES IN UTERINE CANCER

High-Risk Early Stage Disease Adjuvant Therapy Studies

- Aalders studied 540 patients with stage I endometrial cancer status post TAH BSO, but who were not surgically staged. All received brachytherapy and were randomized to WP-XRT or no further treatment (NFT). There was no improvement in OS. The 5 YS was 89% in the EBXRT arm versus 91% in the NFT (NS).

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Vaginal and pelvic recurrences were 6.9% in the NFT arm versus 1.9% if given pelvic XRT. Distant metastasis occurred more often in the XRT arm. In the subset of patients with stage IC grade 3 disease, there were fewer recurrences in the EBXRT arm, 18% versus 7% (47).

- PORTEC 1: 715 eligible patients underwent TAH and BSO without surgical staging or lymphadenectomy. Patients were included if they had either: grade 1 disease with greater than 50% invasion, grade 2 with any invasion, or grade 3 with less than 50% invasion. Less than 2% of histologies were other than endometrioid. Patients were randomized to no additional therapy versus WP-XRT to 46 Gy. The 5Y recurrence rate was 4% versus 14%, favoring XRT ($p < 0.001$) and the 5 YS was 81% versus 85% (NS). Distant metastasis was similar at 7% and 8%. The 8 Y RFS was 68% for both groups. The 8Y OS was 71% in the XRT group and 77% in the control group (NS) due to salvage of relapse in the NFT arm (85% of vaginal recurrences were salvageable). An HIR subgroup was identified: patient age older than 60 years, depth of invasion greater than half myometrial thickness, or grade 2 or 3 tumor. In this HIR group, the recurrence rate was 23% versus 5%, favoring XRT. 73% of recurrences were in the vagina. Survival after recurrence was better for the control group rather than XRT group. For the pelvic recurrence patients, 51% were salvaged if they had not received XRT versus 19% if they had received adjuvant XRT. Stage IB grade 3 patients had higher rates of distant metastasis (15%). A subgroup of patients staged IC grade 3 were not randomized but all received WP-XRT. These patients all had a 5 YS of 58%. A 15-year follow-up report yielded a median follow-up of 13.3 years, with a 5.8% locoregional recurrence in the XRT arm versus 15.5% in the NFT arm. 74% of these recurrences were isolated vaginal recurrences (48-50).
- Systemic pelvic lymphadenectomy randomized trial ILIADE II study: 514 eligible patients underwent hysterectomy with BSO and were randomized to systemic P-LND or no LND. LND improved surgical staging with 13.3% versus 3.2% of patients identified with LN metastasis. At 49 months of follow-up, the 5Y DFS and OS were 81% and 85.9% in the LND arm and 81.7% and 90% in the no LND arm. There was no improvement in DFS or OS with LND. Researchers found the rate of recurrence in LN beds was 1.5% in each arm; therefore, LN basins were not where patients recurred (26).
- GOG 99: 392 eligible patients with type I cancers staged IB, IC, IIA, and occult IIB were evaluated. All were surgically staged with TAH, BSO, pelvic and para-aortic LND. Of patients, 75% had endometrioid histology, 80% had grade 1 or 2 tumors, 25% had LVSI, and 10% were stage II. Patients were randomized to WP-XRT to 50.4 Gy without brachytherapy, or no further therapy (NFT). Median follow-up was 68 months. The overall recurrence rate was 12% in the NFT group and decreased to 3% with XRT. The OS was 86% in the NFT group versus 92% in the XRT arm (NS). A HIR group was identified, which accounted for 132 patients (one third of those enrolled) and two thirds of the study-related deaths. This HIR group included patients of age ≥70 years with one risk factor, age 50 to 69 years with two risk factors, and any age with all three. The risk factors were: outer one-third myometrial

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invasion, grade 2 or 3 tumor, and LVSI. For this subgroup, the recurrence rate was reduced with adjuvant XRT from 26% to 6%. The major difference was the vaginal vault recurrences: 13 recurred vaginally in the NFT versus two that recurred in the XRT arm, and of these two, both had refused XRT. Five percent in each group had distant metastasis (51).

- PORTEC 2: this study evaluated 427 patients with stage I or stage IIA endometrial carcinoma with HIR factors. Patients were randomized to pelvic XRT (46 Gy) or vaginal brachytherapy (21 Gy high-dose rate or 30 Gy low-dose rate). The 5-year vaginal recurrence rate was 1.8% for vaginal brachytherapy versus 1.6% for pelvic XRT. The 5-year rates of locoregional relapse were 5.1% for vaginal brachytherapy and 2.1% for pelvic XRT. There were no differences in overall or disease-free survival. At 126 months, LVSI and unfavorable molecular alterations (TP53-mutation or > 10% L1CAM expression) (HR 8.53, 95% CI: 2.7-27.3) and EBXRT (HR 0.16 95%, CI: 0.04-0.70) were independent prognostic factors for pelvic recurrence and locoregional recurrence (HR 0.37, 95% CI: 0.14-0.95 and HR 6.7, 95% CI: 2.5-17.9, respectively), but not for vaginal recurrence. EBXRT should be considered for patients with HIR cancers and tumor with LVSI (52).
- PORTEC3: a multicenter trial of high-risk endometrial cancer patients randomly allocated (1:1) 686 patients to XRT alone (48.6 Gy) in 1.8 Gy fractions five times a week or chemoradiotherapy consisting of two cycles of concurrent cisplatin 50 mg/m^2 followed by four adjuvant cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2. Inclusion criteria were: surgical staging with TH-BSO and LND, histologically confirmed endometrial carcinoma, with one of the following postoperative FIGO 2009 stages and grade: stage IA with invasion, grade 3 with documented LVSI; stage IB grade 3; stage II; stage IIIA or IIIC; or IIIB if parametrial invasion only; stage IA (with invasion), IB, II, or III with serous or CC histology. The primary endpoints were OS and PFS analyzed in the intention-to-treat population. Median follow-up was 42.3 months. At 12 and 24 months, no significant differences in grade 3 or worse adverse events were found between groups; only grade 2 or higher sensory neuropathy adverse events persisted at 24 months (25 [10%] of 240 patients in the chemoradiotherapy group vs. one [<1%] of 247 patients in the XRT alone group; $p < 0.0001$). OS and PFS results are still pending. (53).
- PORTEC-4: this is a three-arm study that will evaluate approximately 500 patients in a 2:1 fashion with HIR endometrial cancer. Patients are randomized to receive vaginal brachytherapy (either 21 Gy in three fractions vs. 15 Gy in three fractions to 5 mm depth vaginal cuff) versus no additional therapy NAT (third arm). Eligible patients had histologically confirmed endometrioid type endometrial carcinoma, via hysterectomy BSO, FIGO 2009 stage I, with one of the following combinations of substage, age, and grade: stage IA, any age and grade 3 without LVSI; stage IB, age 60 years or above and grade 1 or 2; stage IB, any age, grade 1 and 2 with documented LVSI. NTR3263. Results pending (54).
- RTOG-9708: this was a phase II study in 46 patients with high-risk uterine cancer stages I to III cancer who underwent TAH, BSO, +/– LND. High-risk

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pathologic features were: grade 2/3, DOI greater than 1/2, and cervical stromal involvement, or pelvic confined extrauterine disease. Patients were given adjuvant pelvic XRT to 45 Gy with concurrent cisplatin 50 mg/m^2 on days 1 and 28. Vaginal brachytherapy was given after EBXRT. Four additional cycles of cisplatin 50 mg/m^2 and paclitaxel 175 mg/m^2 were given every 28 days after completion of XRT. The median follow-up was 4.3 years. At 4 years, the locoregional recurrence rate was 4% and distant recurrence rates 19%. OS and DFS rates at 4 years were 85% and 81%, respectively. 4Y rates for survival and DFS for stage III patients were 77% and 72%, respectively. There were no recurrences for patients with stage IC, IIA, or IIB (55).

- Japanese Gynecologic Oncology Group-2033: this study evaluated 385 patients with stage IC to stage IIIC endometrial carcinoma who were randomized to WP-XRT versus cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (CAP chemotherapy) every 4 weeks for three or more courses. The 5Y PFS was nearly the same at 83.5% in the pelvic XRT group and 81.8% in the CAP group. The 5Y OS was 85% in the XRT group versus 87% in the chemotherapy group (NS). A subgroup of HIR patients—who were defined as having (a) stage IC disease in patients over 70 years of age or having grade 3 tumor or (b) stage II or stage IIIA (positive cytology) with greater than 50% myometrial invasion—were found to have significantly better outcomes with chemotherapy: the PFS for the XRT arm was 66% versus 84% for the chemotherapy arm, and the OS was 74% in the XRT group versus 90% in the chemotherapy group (56).
- SEPAL study: Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer: cohorts from two different Japanese gynecologic oncology teams totaling 671 patients were retrospectively analyzed with respect to the use of PA-LND. Routine PA-LND was practiced standardly at one facility and not at the other. Both facilities offered systemic pelvic lymph node dissection (P-LND). A median P-LND count was 34 in the P-LND group versus 59 in the combined PA and P-LND group. Patients at intermediate or high risk of recurrence were offered adjuvant chemotherapy and XRT. The OS was longer in the combination PA and P-LND group with a HR of 0.53. The risk of death was reduced independent of adjuvant therapies so it was recommended that a combined PA and P-LND be performed for all intermediate and high-risk patients (57).
- GOG 249: 601 patients were randomized after TH BSO in a phase III trial of WP-XRT versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk, early stage endometrial cancer. All patients were required to undergo hysterectomy. Staging was encouraged, but not required. All patients had stage I endometrioid disease with GOG 99 based high risk criteria (based on age, tumor grade, depth of invasion, and presence of LVSI), stage II, or stage I and II serous or clear cell tumors. Patients assigned to WP-XRT were treated with standard four-field or intensity-modulated radiation therapy (IMXRT) techniques. Additional VCB was optional for patients with serous or clear cell tumors or stage II disease. Patients assigned to VCB/C received high dose rate (HDR) or low dose rate (LDR) brachytherapy followed by paclitaxel 175 mg/m^2 (3 hours) plus

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carboplatin AUC 6 q21 days for a total of three cycles. Of the 601 patients, 289 received WP-XRT and 291 received VCB/C. The median age was 63 years, 74% had stage I disease, and 89% underwent lymphadenectomy; 71% had endometrioid histology, 15% had serous, and 5% had clear cell. Of patients, 91% completed WP-XRT and 87% completed VCB/C. Recurrence sites totaled 5 versus 3 vaginal, 2 versus 19 pelvic, and 32 versus 24 distant failures with WP-XRT versus VCB/C. With a median follow-up of 24 months, the 24-month RFS was 82% versus 84% for WP-XRT and VCB/C and treatment hazard ratio (HR) was 0.97 (95% CI: 0.635–1.43) (VCB/C relative to WP-XRT). The 24-month survival was 93% versus 92% for WP-XRT and VCB/C and treatment HR was 1.28 (95% CI: 0.689–2.36) (VCB/C relative to WP-XRT). There was no statistically significant treatment effect heterogeneity with respect to RFS among clinical–pathologic variables evaluated. There was higher toxicity in the chemotherapy arm (58).

- MaNGO ILIADE-III NSGO-EC-9501/EORTC-55991: This was a pooled study from two randomized trials evaluating 534 patients with FIGO 1988 staged I-IIIC (pelvic LN only involvement) endometrial cancer. The primary endpoint was PFS. Patients were randomly assigned to adjuvant XRT with or without sequential chemotherapy. Comprehensive surgical staging with LND was not mandatory and 30% did not have LND. Inclusion criteria were serous clear cell or anaplastic tumors by definition. Serous and clear cell tumors were included in the NSGO/EORTC trial only. Optional vaginal brachytherapy was decided before randomization. Pelvic XRT was given before chemotherapy in the combination arm. Chemotherapy consisted of either: 4 courses of doxorubicin/epirubicin 50 mg/m^2 and cisplatin 50 mg/m^2 every 4 weeks; paclitaxel 175 mg/m^2 and epirubicin 60 mg/m^2/doxorubicin 40 mg/m^2 and carboplatin AUC 5; or paclitaxel 175 mg/m^2 and carboplatin AUC 5-6 every 21 days. The PFS difference in the NSGO/EORTC trial favored combination XRT and chemotherapy with HR 0.64 (95% CI: 0.41-99; p = 0.04.) In the MaNGO trial the HR was 0.61 but was NS. When the data was pooled, the HR was 0.63 (95% CI: 0.41-0.99; p = 0.009) favoring combination therapy. The pooled trial data showed significant differences in cancer specific survival with a HR of 0.55 (95% CI: 0.35-0.88; p = 0.01). This trial then showed the sequential use of chemotherapy after XRT was associated with a 36% decrease in the rate of relapse or death and a 49% decrease in the rate in the risk of death from endometrial cancer.
- GOG 258: randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel versus carboplatin and paclitaxel. Results pending.
- RTOG-0921: this was a phase II study of postoperative IMRT with concurrent cisplatin and bevacizumab followed by carboplatin and paclitaxel for patients with endometrial cancer. 30 eligible patients with TH-BSO LND and had ≥1 of the following high-risk factors: grade 3 carcinoma with greater than 50% myometrial invasion, grade 2 or 3 disease with any cervical stromal invasion, or known extrauterine extension confined to the pelvis. Treatment consisted of pelvic IMRT and concurrent 50 mg/m^2 cisplatin on days 1 and 29 of XRT and bevacizumab (at a dose of 5 mg/kg on days 1, 15, and 29 of XRT) followed

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by adjuvant carboplatin AUC 5 and paclitaxel 135 mg/m^2 for four cycles. 23.3% patients developed grade ≥3 treatment-related non-hematologic toxicities within 90 days; an additional six patients experienced grade ≥3 toxicities between 90 and 365 days after treatment. The 2Y OS rate was 96.7% and the disease-free survival rate was 79.1%. No patient developed a within-field pelvic failure and no stage IIIA and lower had recurrent disease with a median follow-up of 26 months (59).

Surgical-pathological findings in type 1 and 2 endometrial cancer: This NRG Oncology/Gynecologic Oncology Group study was a surgical pathological study of uterine adeno carcinoma or carcino-sarcoma cancer patients enrolled in GOG 210. 5,866 patients with extra-uterine disease were evaluated and all uterine histologies were included, with 1,630 of the total being type II tumors. Molecular analysis using data from The Cancer Genome Analysis identified certain predictive proteins: 16% of patients were found to have somatic *BRCA* mutations. Tumors with mutations of either *PTEN* and *BRCA2* were associated with improved survival (96).

Advanced and Recurrent Endometrial Cancer Studies

- GOG 28: this study evaluated melphalan, 5-fluorouracil (FU), and Megace versus doxorubicin, 5-FU and cyclophosphamide in 358 patients with FIGO stages III and IV or recurrent endometrial cancer. The overall response rate (ORR) in those with measurable disease was 38% in both groups; 36% of each group had stable disease, and only 26.4% progressed on treatment. The OS was 10.6 versus 10.1 months, respectively (both NS) (60).
- GOG 48: this study evaluated 356 eligible patients and compared doxorubicin to the doublet of doxorubicin and cyclophosphamide. All patients had received prior therapy with progestins subsequent to progression of disease. A response rate of 22% versus 32% was found and an OS of 6.8 versus 7.6 months was identified with a 17% reduction in the rate of death (61).
- GOG 94: this trial evaluated 77 stage III/IV type I and 103 type II endometrial cancers. A subgroup (phase II study) of patients with stage I/II serous and CC uterine cancer patients were also evaluated. Treatment was whole abdominal radiotherapy (WAR). The 3Y RFS was 29% and 27% for the type I and type II cancers, respectively. The OS were 31% and 35%, respectively. The 5Y PFS was 54%. The OS was 34%. This led to the development of GOG 122 (62,63).
- GOG 107: this study evaluated doxorubicin 60 mg/m^2 versus doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks in 281 eligible patients with stage III/IV or recurrent endometrial cancer. The ORR was 25% versus 42%. The median PFS was 3.8 versus 5.7 months, and the median OS was 9.2 versus 9 months for doxorubicin alone versus the doublet, respectively. The doublet improved RR and PFS with little impact on OS (64).
- GOG 122: this trial randomized 400 patients with stage III, IV, and recurrent disease to WAR versus doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 (AP) for seven cycles plus an additional eighth cycle of cisplatin alone every 3 weeks. Of patients, 85% had a P-LND and 75% had a PA-LND. XRT was dosed at 45 Gy total (30 Gy WAR + 15 Gy boost to the PA LN and to the pelvis). 85% had

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microscopic residual disease, 25% were stage IV, and 50% were stage IIIC. The PFS HR was 0.71 favoring AP demonstrating a 12% decrease in recurrence at 5 years with chemotherapy. The OS HR was 0.68 favoring chemotherapy. A 13% increase in OS was seen at 5 years in the chemotherapy arm. The 5 YS was 53% with chemotherapy versus 42% with XRT (65).

- GOG 139: this trial evaluated a possible circadian difference in the administration of doxorubicin and cisplatin in 342 patients with stages III, IV, and recurrent disease. No benefit was found to timing the administration of chemotherapy based on increased glutathione levels early in the morning. The RR was 46% versus 49%. The PFS was 6.5 months for the standard timed therapy and 5.9 months for the circadian timed therapy. The OS was 11.2 for standard versus 13.2 months for the circadian therapy (both NS) (66).
- GOG 163: this trial evaluated 328 chemotherapy-naïve uterine cancer patients FIGO staged III or IV or recurrent (prior XRT and hormone therapy not excluded), were randomly assigned to doxorubicin 60 mg/m^2 followed by cisplatin 50 mg/m^2 (arm 1, n = 157) or doxorubicin 50 mg/m^2 followed 4 h later by paclitaxel 150 mg/m^2 over 24 h plus filgrastim 5 mcg/kg on days 3-12 (arm 2, n = 160). Both regimens were repeated every 3 weeks for a maximum of seven cycles. There was no significant difference in response rate, PFS, or OS. The odds of response ratio in arm 2 relative to arm 1 stratified by PS was 1.12 [95% CI: 0.69–1.79; $p = 0.36$, one-tailed]. The median PFS was 7.2 months on arm 1 and 6 months on arm 2. The HR relative to arm 1 was 1.01 (95% CI: 0.80–1.28; $p = 0.46$, one-tailed). The median OS was 12.6 months on arm 1 and 13.6 months on arm 2. The death HR relative to arm 1 was 1.00 (95% CI: 0.78–1.27; $p = 0.49$, one-tailed) Toxicities were primarily hematological, with 54% (arm 1) and 50% (arm 2) of patients experiencing grade 4 granulocytopenia. There was no difference in PFS or OS in either group. The response rate was 40% versus 43%; the PFS was 7.2 versus 6 months; and the OS was 12.6 versus 13.6 months (NS) (67).
- GOG 177: this study looked at the combination of paclitaxel 160 mg/m^2, doxorubicin 45 mg/m^2, and cisplatin 50 mg/m^2 (TAP) with G-CSF support versus the doublet of doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 (AP): 273 patients with stage III, IV, or recurrent disease were treated every 3 weeks for seven cycles or until progression; 50% of patients on both arms received all cycles of therapy. There was a 22% complete response (CR) in the TAP arm versus a 7% CR on the AP arm and a PR of 36% versus 27%. The overall response rates were 57% versus 34%, the PFS was 8.3 versus 5.3 months, and the median OS was 15.3 versus 12.1 months, all favoring TAP (68).
- GOG 184: in this study, 552 eligible patients with stages III and IV disease were randomized to receive chemotherapy consisting of the triplet of cisplatin 50 mg/m^2, doxorubicin 45 mg/m^2, and paclitaxel 160 mg/m^2 (TAP) versus the doublet of cisplatin and doxorubicin (AP) at the same dosing for six cycles after volume directed XRT. 80% completed six cycles of chemotherapy. No difference in OS was found. The PFS was 64% for the TAP versus 62% for the AP arm HR 0.9 95% CI: 0.69-1.17 $p = 0.21$, one-tail). A subgroup analysis found that TAP

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was associated with a 50% reduction in recurrence or death if there was gross residual disease (69).

- GOG 209: this noninferiority trial compared carboplatin AUC 6 and paclitaxel 175 mg/m^2 given every 3 weeks for seven cycles to paclitaxel 160 mg/m^2, doxorubicin 45 mg/m^2, and cisplatin 50 mg/m^2 (TAP) with G-CSF support every 3 weeks for seven cycles in 1,312 patients with metastatic or recurrent endometrial cancer. Patients were allowed to receive volume directed XRT. A 14-month RFS was found in each arm (HR: 1.03), with an OS of 32 months versus 38 months, respectively (HR: 1.01). The neurotoxicity was 26% versus 19% favoring carboplatin and paclitaxel, thus this regimen is not inferior to TAP (70).
- GOG 238: this was a randomized trial of pelvic XRT with or without concurrent weekly cisplatin in patients with pelvic only recurrence of carcinoma of the uterine corpus. The two arms were: a) WP-XRT dosed at 4500 cGy in 25 fractions with interstitial or intracavitary brachytherapy or an external beam boost versus b) WP-XRT 4500 cGy in 25 fractions with weekly cisplatin at 40 mg/m^2 with interstitial or intracavitary brachytherapy or an external beam boost. Results pending.
- XRT salvage for vaginal recurrent disease: whole pelvic and HDR brachytherapy were used: 45 Gy of WP-XRT was delivered in 25 fractions and VB was given to a median dose of 23.75 Gy in five fractions. Complete clinical response (CCR) was seen in 95% of patients. 5Y local control, distant control, RFS, and OS were 95%, 61%, 68%, and 67%, respectively (71).
- Mundt et al found evidence to support the continued use of locoregional XRT in combination with chemotherapy for high-risk stage III/IV patients. 43 patients were reviewed retrospectively. Patients treated with doxorubicin and platinum chemotherapy alone were found to have a 67% incidence of recurrence; 31% relapsed in the pelvis, vagina, or both, making the case for adding radiation therapy for multimodality therapy (72).
- GOG 129F: single-agent paclitaxel was evaluated in a phase II trial for patients with persistent or recurrent endometrial cancer. Paclitaxel was dosed at 200 mg/m^2, and 175 mg/m^2 for patients with prior WP-XRT, every 3 weeks. A 27.3% overall RR was seen in 44 patients (73).
- GOG 139S: this study evaluated histology among different uterine cancer studies totaling 1,203 patients from four randomized trials. The response with different combinations of doxorubicin, cisplatin, and paclitaxel was not associated with histology except for the CC subtype (ORR for type I was 44%; type II serous, 44%; type II CC, 32%). A main predictor of OS was histology with the type II tumors having a HR of 1.2 for serous and 1.5 for CC carcinoma. The breakdown of histology by GOG study is: GOG 122 had 50% endometrioid, 20% serous, 5% CC, and 10% mixed histologies, 80% were grade 2, 3; GOG 177 had 15% and 19% serous in each arm; GOG 184 had 13% serous in each arm; GOG 99 had none (74).
- MITO-END2: this trial included 108 patients with advanced or recurrent endometrial cancer who had received 0 to 1 prior lines of chemotherapy. Bevacizumab was added to six to eight cycles of carboplatin and paclitaxel and then continued as maintenance therapy. This approach resulted in a significant

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improvement in median PFS (13 vs. 8.7 months, $p = 0.036$) and a numerical increase in median OS (23.5 vs. 18 months, $p = 0.24$), although these OS data are not yet mature (75).

- GOG 229H: phase II study of cediranib, a multitargeted tyrosine kinase inhibitor (VEGF/PDGF/FGF) in endometrial cancer. 48 evaluable patients were administered single-agent cediranib 30 mg PO daily for a 28-day cycle. The median age was 65.5 years, 52% of patients had received prior XRT, and 73% of patients received only one prior chemotherapy regimen. PR was seen in 12.5%, 29% had a 6-month event free survival (EFS). The median PFS was 3.65 months and median OS was 12.5 months (43).
- Lenvatinib: a phase II trial of 133 patients with recurrent disease found a RR of 22%, with 44% having SD and a median duration of response of 9 months (76).

MMMT-Carcinosarcoma Trials

- GOG 108: 194 patients with stages III/IV and recurrent disease were randomized between ifosfamide versus ifosfamide and cisplatin. The response rate was 36% versus 54%. The PFS was 4 months versus 6 months with a RR of response 0.73 ($p = 0.02$). PFS and survival data suggest that the combination offers a slight prolongation of PFS (RR, 0.73; 95% upper CI: 0.94; $p = 0.02$, one-tailed test), but not significant for OS (RR, 0.80, 95% CI: 1.03; $p = 0.071$, one-tailed test) (77).
- GOG 150: this trial evaluated 206 patients with stage I to IV optimally debulked carcinosarcoma, and randomized them to WAR with a pelvic boost versus ifosfamide with mesna and cisplatin. The recurrence rate was 58% in the WAR arm versus 52% in chemotherapy arm (NS). There was a significant survival benefit to chemotherapy (HR 0.67) with a 5 YS of 47% versus 37%. Recurrence was vaginal in 3.8% of patients who received WAR compared to 9.9% in the chemotherapy arm. The final recommendation was that chemotherapy and vaginal brachytherapy may be the best combination for carcinosarcoma (38).
- GOG 161: this trial evaluated 179 patients with stage III/IV, persistent, or recurrent disease. Ifosfamide/mesna dosed at 1.6 g/m^2 IV daily for 3 days plus paclitaxel 135 mg/m^2 every 3 weeks was compared to ifosfamide/mesna 2 g/m^2 IV daily for 3 days every 3 weeks up to eight cycles. A higher RR of 45% was seen with the doublet compared to 29% with the single agent. The PFS was found to be significant at 5.8 versus 3.6 months (a 31% decrease in the HR of death 0.69; 95% CI: 0.49-0.97, $p = 0.3$), as was the OS of 13.5 versus 8.4 months (HR 0.71; 95% CI: 0.51-0.97, $p = 0.3$), both favoring the doublet (78).
- GOG 261: stages I-IV and recurrent uterine MMMT (also including TOC and peritoneal MMMT), chemotherapy naïve patients are randomized in a phase III noninferiority trial to ifosphamide 1.6 g/m^2 days 1,2,3 and paclitaxel 135 mg/m^2 versus carboplatin AUC 6 and paclitaxel 135 mg/m^2. Cycles are every 3 weeks for 6 to 10 cycles. Results pending.
- SEER study: 1,891 patients with stages I and II MMMT demonstrated that pelvic XRT was associated with a 21% reduction in cancer specific mortality. For

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patients who did not have an LND, radiation therapy was associated with a 25% reduction in mortality (7).

- EORTC 55874: this was a phase III randomized trial for 224 patients of adjuvant pelvic XRT versus observation for all early stage sarcomas. There were 103 LMS, 91 MMMT, and 28 ESS. All patients underwent TAH and BSO and washings (166 patients): nodal sampling was not required and 25% had an LND. Patients were randomized to either observation or pelvic XRT, 51 Gy in 28 fractions over 5 weeks. 112 patients were in each arm. A reduction in local relapse (14 vs. 24, $p = 0.004$) was seen but no effect on either OS or PFS was seen. The MMMT patients trended toward better local control versus LMS patients, but they had a higher rate of distant metastasis and there was no change in OS with additional XRT (79).
- TOTEM: **T**rial **O**f **T**wo follow up regimens in **E**ndo**M**etrial cancer: this is a study evaluating two follow-up regimens with different test intensity in endometrial cancer-treated patients: does a more intensive routine investigation lead to a survival advantage. Results pending.
- FIGURE: follow-up In Gynecological Care Units: addressing whether a routine compared with patient-initiated follow-up strategy is superior. Results pending.
- ENDAT: endometrial cancer telephone follow-up trial: assessing whether a nurse-led telephone follow-up is as beneficial as standard follow-up care. Results pending.

UTERINE SARCOMAS

I. Characteristics
   - Sarcomas arise from the mesodermal tissues of the body. In gynecology, they most commonly originate in the uterus.
   - Sarcomas are estimated to comprise 5%-6% of the total 61,380 uterine cancers in 2017 in the United States. There is a 3% risk of adnexal metastasis (80).
   - Clinically patients can present with postcoital bleeding, intermenstrual bleeding, an enlarged uterus, or the cancer can mimic a prolapsed fibroid on examination.
   - The main risk factor is a history of prior pelvic XRT.
   - The route of spread can be lymphatic, peritoneal, or hematogenous.

II. Pre-treatment workup includes an EMB or D&C, a CXR, CT of the abdomen and pelvis, and consideration of a chest CT if there is a confirmed diagnosis of sarcoma. 19% of patients with LMS have lung metastasis. Routine preoperative lab tests are important.

III. Staging is surgical. This includes hysterectomy, BSO, exploration of the abdomen and pelvis, possible LND, biopsy of any suspicious extrauterine lesions, and omentectomy. Histology was updated in 2014. It differentiates **LMS**, low-grade and high-grade **ESS**, and undifferentiated sarcoma from adenosarcomas (ASs) (81).

- Staging for LMS and ESS was last amended by FIGO in 2009 (Table 2.20A–D).

Stage I: tumor limited to uterus
   - IA: < 5 cm
   - IB: > 5 cm

Stage II: tumor extends to the pelvis
   - IIA: adnexal involvement
   - IIB: extrauterine pelvic tissue

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Stage III: abdominal involvement
- IIIA: invades the abdomen 1 site
- IIIB: invades the abdomen > 1 site
- IIIC: involvement of pelvic and/or para-aortic LN

Stage IV:
- IVA: involves bladder or rectum
- IVB: distant metastasis (Table 2.21A–D)

Table 2.20A AJCC Staging 8th Edition for ESS and LMS: T Category

T	FIGO	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

ESS, endometrial stromal sarcoma; LMS, leiomyosarcoma.

Table 2.20B N Category

N	FIGO	N criteria
NX		Regional LNs cannot be assessed
N0		No reginal LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) no greater than 0.2 mm
N1	IIIC	Reginal LN metastasis

LN, lymph node.

Table 2.20C M Category

M	FIGO	M criteria
M0		No distant metastasis
M1	IVB	Distant mestasis

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Table 2.20D Stage Grouping			
When T is	**And N is**	**And M is**	**The stage group is**
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T1c	N0	M0	IC
T2	N0	M0	II
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1	M0	IIC
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

- FIGO staging for adenosarcoma (AS) Table 2.21A

Table 2.21A AJCC Staging 8th Edition for AS: T Category		
T	**FIGO**	**T criteria**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor limited to the endometrium/endocervix
T1b	IB	Tumor invades less than half of the myometrium
T1c	IC	Tumor invades more than half of the myometrium
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

AS, adenosarcoma.

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Table 2.21B N Category

N	FIGO	N criteria
NX		Regional LNs cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional LN(s) no greater than 0.2 mm
N1	IIIC	Regional LN metastasis

LN, lymph node.

Table 2.21C M Category

M	FIGO	M criteria
M0		No distant metastasis
M1	IVB	Distant metastasis

Table 2.21D Stage Grouping

When T is	And N is	And M is	The stage group is
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1	M0	IIIC
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

IV. There are four main histologic types of uterine sarcoma: LMS, low-grade and high-grade ESS, and undifferentiated sarcoma. More uncommon uterine sarcoma subtypes are AS, PEComa, and rhabdomyosarcoma.

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- LMS is the most common uterine sarcoma. It originates from the uterine smooth muscle. It represents 40% of uterine sarcomas. It can present at any age but most commonly arises in women aged 45 to 55 years old. Only 15% are diagnosed preoperatively with an EMB or D&C. For diagnosis, it is necessary to demonstrate coagulative necrosis. One or both of the following are also necessary: cellular atypia, or more than 10 mitosis/HPF. The rate of ovarian metastasis is 3% (82) and the rate of LN metastasis is 6.6% to 11% (83,84). LND has not shown to be of benefit for staging as up to 70% of women with positive LN already have extrauterine disease (85). Ten percent have pulmonary metastasis at presentation so a baseline CXR or chest CT at diagnosis is indicated. BSO has not been shown to reflect on outcome. Adjuvant pelvic XRT reduces local recurrence but does not change OS.
  - If an LMS is found incidentally after hysterectomy, a second staging surgery should be considered if there was morcellation of the uterus; a supracervical hysterectomy was performed initially (in these cases, the cervix should be removed on reoperation), or there was no evaluation of the abdomen or pelvis. A second staging surgery for an LND or BSO has not been found to be beneficial (86).
  - Adjuvant therapy is considered based on stage. Chemotherapy can consist of single-agent doxorubicin with a RR of 25%, single-agent ifosfamide with an RR of 17%, combination ifosfamide and doxorubicin with an RR of 30%, or combination gemcitabine and docetaxel with an RR of 53%. Aromatase inhibitors can be considered if the tumor is ER positive.
    - **Stage I:** observe or consider chemotherapy
    - **Stage II, III:** consider chemotherapy and/or tumor directed EBXRT
    - **Stage IVA:** chemotherapy and/or EBXRT
    - **Stage IVB:** chemotherapy with/without palliative EBXRT
  - For isolated lung recurrences, thoracotomy with resection can yield a survival benefit. The 5 YS was 43% in one series (87).
- **Low-grade ESS:** it is commonly diagnosed in women aged 42 to 53 years. This tumor represents about 8% of uterine sarcomas and arises from the stromal cells between the endometrial glandular cells. LGESS are characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium. Mitotic activity is usually low (<5 MF/10 HPF). It cannot be diagnosed by D&C. Final pathology needs to document LVSI and invasion. If one of these two components is absent, then the diagnosis is an endometrial stromal nodule. There is a 20% risk of pelvic LN metastasis, so consideration for a LND should be entertained. Removal of the ovaries is recommended as these are hormone-dependent cancers and can respond to endogenous estrogen. Reoperation for BSO and LND, if ESS was an incidental finding should be performed if the ovaries were not initially resected. Stage is the most important prognostic factor. Adjuvant therapy is considered based on stage.
  - For stage I, consider observation versus hormonal therapy.
  - For stages II, III, and IVA: hormone therapy with/without tumor directed XRT. 20% of recurrences have been documented in the pelvis.

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    - For stage IVB, consider hormonal therapy with or without palliative XRT.
    - Hormonal therapy can include: Megace (40–160 mg daily); an 88% RR with a 50% CR has been seen (88). Aromatase inhibitors and gonadotropin-releasing hormone (GnRH) agonists may also be considered. Estrogen replacement therapy may increase the chance of recurrence. For recurrent disease, a 33% response rate was seen with ifosfamide and doxorubicin. Aromatase inhibitors can also be considered in these tumors.
    - **Radiation:** there are data to show that 33.3% of recurrences are pelvic only, if no adjuvant XRT was given—so pelvic XRT can be considered.
- **High-grade ESS:** it is characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity (>10 MF/10 HPF). HGESS can contain areas of conventional LGESS. Adjuvant therapy is based on stage:
    - Stage 1: observe or consider chemotherapy.
    - Stage II, III: consider chemotherapy and/or EBXRT.
    - Stage IVA: chemotherapy and/or EBXRT.
    - Stage IVB: chemotherapy with/without palliative EBXRT.
- **Undifferentiated uterine sarcomas (UUS)** are characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of determination. Adjuvant therapy is based on stage: chemotherapy should be considered with a single agent or combination agents to include: doxorubicin, ifosfamide, cisplatin, gemcitabine, and docetaxel. Responses to chemotherapy can occur but at low rates.
    - Stage I: observe or consider chemotherapy.
    - Stage II, III: consider chemotherapy and/or tumor directed EBXRT.
    - Stage IVA: chemotherapy and/or EBXRT.
    - Stage IVB: chemotherapy with/without palliative EBXRT.
- WHO 2003 uterine sarcoma classifies ESS as a category into itself, removing LG and HG. HG is termed undifferentiated endometrial sarcoma. This is slightly different from NCCN terminology (97).
- **Adenosarcoma**: represents 1% of uterine sarcomas. The median age of diagnosis is 50 years old. Abnormal bleeding is common and speculum examination can visualize tumor in 50% of cases. These are mixed tumors with sarcomatous stroma and benign epithelium with a favorable prognosis unless sarcomatous overgrowth or stromal invasion is present. They stain for CD10 and express ER/PR. Extrauterine disease occurs in 20% of cases, staging is appropriate, and BSO should be considered. These are low-grade malignancies, and if recur do so locally. Those with sarcomatous overgrowth may have distant metastasis. 20% can recur more than 5 years after surgery. There is an increased risk of recurrence if deep myometrial invasion is present. Adjuvant XRT and chemotherapy for the subsets of sarcomatous overgrowth or deep stromal invasion can be considered. Ifosfamide, plus doxorubicin, and/or cisplatin or gemcitabine plus docetaxel have produced a few responses for metastatic or recurrent disease. Consider XRT and chemotherapy for sarcomatous overgrowth, heterologous elements, or deep stromal invasion.
    - **Prognostic factors:** stage is the most important prognostic factor; the depth of myometrial invasion, LVSI, grade, histology, tumor size, patient age, and hormone receptor status can all affect outcome (Tables 2.22–2.24).

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5Y SURVIVAL

Table 2.22 Uterine LMS 5 YS

Stage	5Y LMS survival (%)
Localized	63
Regional	36
Distant	14

LMS, leiomyosarcoma; YS, year survival.

Table 2.23 Uterine ESS 5 YS

Stage	5Y ESS survival (%)
Localized	99
Regional	94
Distant	69

ESS, endometrial stromal sarcoma; YS, year survival.

Table 2.24 Uterine Undifferentiated Sarcoma 5 YS

Stage	5Y undifferentiated survival (%)
Localized	70
Regional	43
Distant	23

FOLLOW-UP

- Every 3 months for the first 2 years
  - Every 6 months for the next 3 years
  - Annual examinations thereafter
- Physical and pelvic examination should occur at each visit. Pap smears have not been found to increase the detection of recurrence. CT imaging of the chest/abdomen/pelvis can occur every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, then annually for high-grade sarcomas.

RECURRENT DISEASE

- Local recurrence in the vagina or pelvis with negative CT of the chest/abdomen/pelvic:
  - If prior XRT:
    - Surgical exploration and resection with/without IOXRT with/without systemic therapy *or*
    - Systemic therapy *or*
    - Tumor directed re-irradiation

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  - If no prior XRT:
    - Surgical exploration with resection and/or IOXRT
    - Tumor directed XRT with/without systemic therapy can also be offered
- Isolated distant metastasis:
  - If resectable: consider resection or ablative therapy and consider postoperative systemic therapy with/without EBXRT
  - If unresectable: consider systemic therapy and/or tumor directed EBXRT or local ablative therapy. If there is a response, surgical resection can be considered
- If disseminated disease:
  - Systemic therapy with/without palliative radiation therapy *or*
  - Best supportive care

NOTABLE STUDIES IN SARCOMA

- ESS: in a retrospective review, overall there was a 64% recurrence. The 10Y PFS was 43%, with an OS of 85%. Those who received HRT had ORR of 27% and 53% had stable disease with a median TTP of 24 months. 89% of those without BSO had recurrence, 55% who had a BSO did not recur; 32% had LVSI so LND may be beneficial (89).
- Another retrospective study evaluated ESS stage I and II. There were no relapses in those who received adjuvant XRT, 13 of 30 relapsed if no XRT was administered. Thus pelvic EBXRT may improve local control but may not affect OS (90).
- GOG 277: this was a phase III, double-blind, placebo-controlled trial in patients with chemotherapy-naive, metastatic, unresectable uterine leiomyosarcomas. 107 patients were enrolled, 54 were randomized to gemcitabine–docetaxel plus placebo and 53 to gemcitabine–docetaxel plus bevacizumab. Accrual was stopped early for futility. The gemcitabine–docetaxel—placebo group compared to the gemcitabine–docetaxel—bevacizumab group had median PFS of 6.2 months and 4.2 months, respectively (HR 1.12; $p = 0.58$). Objective responses were seen in 31.5% in the gemcitabine–docetaxel—placebo group and 35.8% in the gemcitabine–docetaxel—bevacizumab group. The mean response duration was 8.6 months vs 8.8 months. The median OS was 26.9 months vs 23.3 months (HR 1.07; $p = 0.81$).
- PALETTE: patients with metastatic soft tissue sarcoma (STS) (all sites) in a multicenter, international, double-blind, placebo-controlled phase III trial that were angiogenesis inhibitor-naïve, and had failed at least one anthracycline containing regimen, were eligible. A total of 369 patients were randomized (246 pazopanib, 123 placebo), 2:1 to receive either pazopanib 800 mg once daily or placebo until tumor progression, unacceptable toxicity, death, or patient's request. The median age was 56. Median duration of follow-up at clinical cut-off date was 15 months. The primary endpoint was PFS. PFS was significantly prolonged with pazopanib (median 20 versus 7 weeks; HR 0.31; 95% CI: 0.24–0.40; $p < 0.0001$). The interim analysis for OS showed a not statistically significant (NS) improvement of pazopanib versus placebo (median: 11.9 vs. 10.4 months; HR 0.83; 95% CI: 0.62–1.09). Main grade 3

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to 4 toxicities in the pazopanib versus placebo arm were respectively: fatigue (13%, 6%), hypertension (7%, nil), anorexia (6%, nil), diarrhea (5%, 1%), thromboembolic events (grades 3–5) (3%, 2%), left ventricular ejection fraction (LVEF) decrease of greater than 15% (8% and 3%). Thus, pazopanib is an active drug in anthracycline pre-treated metastatic STS patients with an increase in median PFS of 13 weeks (92).

- SAR-3007: a subgroup analysis of recurrent uterine LMS patients after prior chemotherapy evaluating trabectedin versus dacarbazine (DTIC). This phase III study randomized in a 2:1 fashion 577 LMS and liposarcoma patients; 140 uterine LMS patients were in the trabectedin arm versus 81 uterine LMS in the DTIC group. Dosing was 1.5 mg/m^2 as a 24-hour infusion for every 3 weeks versus DTIC 1 g/m^2 IV every 3 weeks. The PFS was 4.2 months versus 1.5 months with the OS was 13.4 versus 12.9 for trabectedin versus DTIC, respectively (93).
- Study 309: this trial randomized 452 sarcoma patients to eribulin 1.4 mg/m^2 IV days 1 and 8 q21 days or DTIC 850–1200 mg/m^2 IV day 1 q21 days until progression. 228 patients were randomized to eribulin and 224 patients were given DTIC. OS in the DTIC group was a median of 13.5 months compared to 11.5 months in the eribulin group (95% CI: 10.9–15.6; HR 0.77; 95% CI: 0.62–0.95; $p = 0.0169$). Adverse effects were seen in 97% of those in the DTIC group and 99% in the eribulin group (94).
- From the PALETTE and EORTC 62043 trials: 44 uterine sarcoma patients who were treated with pazopanib were reviewed; 61.3% were heavily pretreated with greater than two lines of chemotherapy; 11% had a partial response. Median PFS was 3 months, median OS was 17.5 months. Response to pazopanib was similar for uterine sarcoma compared to nonuterine STS (95).

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Vulvar Cancer

CHARACTERISTICS

- Vulvar cancer represents 3% to 5% of all female genital cancers and 1% of all malignancies in women. In 2017, there are 6,020 new cases and 1,150 deaths predicted to occur. The average age at diagnosis is 65 years, although it is trending toward a younger age.
- Clinical features include pruritus, ulceration, or a mass. The most common location of lesions is the labia majora (40%), the labia minora (20%), periclitoral region (10%), and perineal area (15%). The route of spread is either by direct extension, lymphatic embolization to the groin nodes, or lymphatic or hematogenous spread to distant sites.
- Risk factors are multifactorial: age greater than 70 years, lower socioeconomic status, hypertension, diabetes, prior lower genital tract dysplasia or cancer, immunosuppression, and human papillomavirus (HPV) infection are known to increase the risk of vulvar cancer. Vulvar SIL/dysplasia is the precancerous state and 76% of patients with vulvar HSIL are HPV positive. There is a 22% rate of subclinical invasive disease in vulvar HSIL, usually less than 1 mm DOI (31).
- Groin lymph node (LN) metastasis: subclinical LN metastasis can occur in 10% to 36% of normally palpated groins (1). Clinical staging clearly under-stages patients. On the contrary, 20% of palpably enlarged LNs are pathologically negative; 28% of patients with positive groin LNs will have positive pelvic LNs.
- The risk for nodal metastasis is related to both depth of invasion and tumor size. The risk of positive LNs with 1 mm DOI is minimal at less than 1%. For a DOI of 2 mm, the risk is 7% to 8%. For a DOI of 3 mm, the risk is 12% to 17%. For a DOI of 5 mm, there is a 15% to 17% risk of LN metastasis. The risk of LN metastasis by lesion size is significant: for a size of 0 to 1 cm, there is a 7.7% risk of positive LNs; for a 2-cm lesion, the risk is 22%; for a 3-cm lesion, the risk is 27%; and for a 5-cm lesion, the risk is 35% to 40% (2).

HISTOLOGY

- Squamous cell carcinoma represents 85% of all vulvar cancers. Other histologic types are basal cell carcinoma, adenocarcinoma, sarcoma, and verrucous carcinoma and melanoma.
- Malignant melanoma represents 5% of vulvar cancers. There are four histologic subtypes of melanoma: superficial spreading, lentigo, acral, and nodular.
- Vulvar Paget's disease has cutaneous and noncutaneous (bladder/colorectal) subtypes. Underlying invasive adenocarcinoma is present in 4% to 17% of cases; 30% to 42% of patients may have, or will later develop, an adenocarcinoma at another nonvulvar location such as the breast, rectum, colon, or uterus.

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- Grading: FIGO grading is the most commonly used grading system and is as follows:
  - G1: Well differentiated
  - G2: Moderately differentiated
  - G3: Poorly or undifferentiated.

  GOG grading in vulvar cancer is slightly different than for other tumors. G1 tumors are well differentiated, G2 tumors are composed of less than one third of G3 cells. G3 tumors are composed of greater than one third yet less than one half of G3 cells. G4 tumors have greater than one half of the tumor composed of G3 cells.
- The depth of invasion is measured from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

PRE-TREATMENT WORKUP

- Pre-treatment workup includes a physical exam with careful evaluation of the vagina and cervix. Five percent of invasive lesions are multifocal. Biopsy for diagnosis should occur at the center of any suspicious area.
- Imaging with CT, MRI, or PET can be obtained if positive groin or pelvic LNs are suspected. Chest x-ray should be obtained, as well as standard lab tests. EUA with cystoscopy can assist in determination of the extent of an anterior lesion's involvement of the urethra. Proctoscopy can be helpful in determination of anorectal involvement if there is a large lesion impinging on the posterior perineal triangle.
- Single-photon emission computed tomography with CT (SPECT/CT) for sentinel lymph node detection (SLND) has been shown to improve SLN dissection by preoperative three-dimensional anatomical localization. In preoperative imaging, SPECT/CT was shown to identify more SLNs (mean 8.7 LN per patient) versus lymphoscintigraphy (mean 5.9) and led to high spatial resolution and anatomical localization. It also identified aberrant lymphatic drainage in 17.5% of patients. Aberrant sentinel lymph nodes were found in the following locations: 31.7% pelvic, 2% paravesical, 7.5% para-aortic, 2% gluteal. Sensitivity for all who underwent complete groin LND was 100%, NPV 100%, the FN rate was 0%. For dissection, distances were calculated from the ASIS or symphysis based on SPECT/CT (3).
- If the groin LNs appear positive, FNA can be considered before a groin LND. If cytology from the FNA is positive, then aggressive surgical removal of bulky LNs should be considered because the usual doses of EBXRT are not adequate to control large volume disease. There is no need to perform a complete LND in light of bulky LNs; instead, remove the bulky disease and mark the area with hemoclips before XRT. If the LNs are fixed and unresectable, consider neoadjuvant chemotherapy and XRT.
- The workup for melanoma is CT of the chest/abdomen/pelvis, MRI of the brain, LDH, and baseline PET. *BRAFV600E* gene mutation information should be obtained via IHC on the tumor.

STAGING

- Vulvar cancer is staged **surgically** and last updated by FIGO in 2009. FIGO modifies the staging systems and the TNM categories have been defined to correspond to the FIGO stages; however there are notable differences between FIGO staging and AJCC staging for positive lymph node status (Table 2.25) (Table 2.26A–D).

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Table 2.25 2009 FIGO Staging: Carcinoma of the Vulva

FIGO stage	Description
Stage I	Tumor confined to the vulva and/or perineum. Multifocal lesions should be designated as such.
• IA	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less
• IB	Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and/or perineum
Stage II	Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement) with negative nodes
Stage III	Tumor of any size with or without extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement) with positive inguino-femoral lymph nodes
• IIIA(i) • IIIA(ii) • IIIB(i) • IIIB(ii) • IIIC	One LN metastasis ≥ 5 mm One or two LN metastases each < 5 mm Two or more LN metastasis ≥ 5 mm Three or more LN metastasis < 5 mm LN(s) with extranodal extension
Stage IV	Tumor of any size with extension to any of the following or distant structures:
• IVA(i)	Tumor invading upper/proximal two thirds of the urethra, upper/proximal two thirds of the vagina, bladder mucosa, or rectal mucosa, or fixed to the pelvic bone
• IVA(ii)	Fixed or ulcerated regional LN metastasis
• IVB	Distant metastasis (including pelvic LN metastasis)

Source: International Federation of Gynecology and Obstetrics.

Table 2.26A AJCC 8th Edition: T Category

T	FIGO stage	T criteria
Tx		Primary tumor cannot be assessed
T0	I	Tumor confined to the vulva and/or perineum. Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. Depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion
T1a	IA	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less

(*continued*)

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Table 2.26A AJCC 8th Edition: T Category (*continued*)

T	FIGO stage	T criteria
T1b	IB	Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and/or perineum
T2	II	Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement)
T3	IVA(i)	Tumor of any size with extension to any of the following: upper/proximal two thirds of the urethra, upper/proximal two thirds of the vagina, bladder mucosa, or rectal mucosa, or fixed to the pelvic bone

Table 2.26B AJCC 8th Edition: N Category

N	FIGO stage	N criteria
NX		Regional LNs cannot be assessed
N0		No regional LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) no greater than 0.2 mm
N1	III	Regional LN metastasis with one or two LN metastasis each <5 mm, or one LN metastasis ≥5 mm
N1a	IIIA	One or two LN metastases each <5 mm
N1b	IIIA	One LN metastasis ≥5 mm
N2		Regional LN metastasis with three or more LN metastases, each <5 mm, or two or more LN metastases ≥5 mm, or LN(s) with extranodal extension
N2a*	IIIB	Three or more LN metastases each <5 mm
N2b	IIIB	Two or more LN metastases each ≥5 mm
N2c	IIIC	LN(s) with extranodal extension
N3	IVA(ii)	Fixed or ulcerationed regional LN metastasis

LN, lymph node.
*Includes micrometastasis N1mi and N2mi.

Table 2.26C AJCC 8th Edition: M Category

M	FIGO stage	M criteria
M0		No distant metastasis (no pathological M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis (including pelvic LN metastasis)

LN, lymph node.

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Table 2.26D AJCC 8th Edition: Stage Grouping

When T is	And N is	And M is	The stage group is
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T1–2	N1–2c	M0	III
T1–2	N1a, N1b	M0	IIIA
T1–2	N2a, N2b	M0	IIIB
T1–2	N2c	M0	IIIC
T1–3	N3	M0–M1	IV
T1–2	N3	M0	IVA(ii)
T3	Any N	M0	IVA(i)
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

- Melanoma is surgically staged in a similar fashion. There are a few different methods of staging. Stage is the most important prognostic factor. Breslow's staging is used by the AJCC because it is more reproducible and better for ulcerated lesions.
  - Stage:

Stage	Clark's level	Chung's level	Breslow's level/depth
I	Intraepithelial	Intraepithelial	<0.76 mm
II	Papillary dermis	<1 mm from granular layer	0.76–1.5 mm
III	Fills dermal papillae	1.1–2 mm from granular layer	1.51–2.25 mm
IV	Reticular layer	>2 mm from granular layer	2.26–3 mm
V	Subcutaneous fat	Subcutaneous fat	>3 mm

  - Chung's staging has replaced Clark's staging because it did not take into account that vulvar skin is non–hair-bearing and contains less subcutaneous tissue.
    - **Stage Grouping** Table 2.27D
    - **Mitotic rate** assessment: a higher mitotic rate is porportional to growth and spread (Tables 2.27A-E and 2.28).

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Table 2.27A AJCC 8th Edition Staging: Melanoma T Category

T	Thickness	Ulceration status
TX: primary tumor thickness cannot be assessed (diagnosis was by curettage)	NA	NA
T0: no evidence of primary tumor (unknown primary or completely regressed)	NA	NA
Tis: (melanoma in situ)	NA	NA
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration 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

Table 2.27B AJCC 8th Edition Staging: N Category

N	Number of tumor-involved regional LN (s)	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (SLND not performed, regional nodes previously removed for unrelated reason. Exception: pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	No
N1a	One clinically occult LN (i.e., detected by SLND)	No

(*continued*)

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Table 2.27B AJCC 8th Edition Staging: N Category (*continued*)

N	Number of tumor-involved regional LN (s)	Presence of in-transit, satellite, and/or microsatellite metastases
N1b	One clinically detected LN	No
N1c	No regional LN disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLND)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLND)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

LN, lymph node; SLND, sentinel lymph node dissection.

Table 2.27C AJCC 8th Edition Staging: M Category

M	M criteria/anatomic site	LDH level
M0	No evidence of distant metastasis	NA
M1	Evidence of distant metastasis	See the following
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional LN	Not recorded or unspecified
M1a (0)		Not elevated
M1a (1)		Elevated

(*continued*)

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Table 2.27C AJCC 8th Edition Staging: M Category (*continued*)		
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b (0)		Not elevated
M1b (1)		Elevated
M1c	Distant metastasis 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 metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d (0)		Normal
M1d (1)		Elevated
Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

Table 2.27D AJCC 8th Edition Staging: Clinical Stage Grouping (cTMN)

When T is	And N is	And M is	Then the clinical stage group is
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	Ib
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV
Tis	N0	M0	0
T1a	N0	M0	IA

Table 2.27E AJCC 8th Edition Staging: Pathological Stage Grouping (pTNM)

When T is	And N is	And M is	Then the pathological stage group is
T1b	N0	M0	IA
T2a	N0	M0	Ib
T2b	N0	M0	IIA
T3a	N0	M0	IIA

(*continued*)

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Table 2.27E AJCC 8th Edition Staging: Pathological Stage Grouping (pTNM) (*continued*)

When T is	And N is	And M is	Then the pathological stage group is
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1 b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥ N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

Table 2.28 5Y Survival (YS) for Melanoma

Stage	5 YS for Melanoma
IA	5 YS rate of 95%
IB	5 YS rate of approximately 91%
IIA	5 YS rate of 77%–79%
IIB	5 YS rate of 63%–67%
IIC	5 YS rate of 45%
IIIA	(T1-4aN1aM0) have a 5 YS rate of 70% ; (T1-4aN2aM0) 5 YS rate of 63%
IIIB	(T1-4bN1aM0) or (T1-4bN2aM0) have a 5 YS rate of 50%–53%; (T1-4aN1bM0) or (T1-4aN2bM0) have a 5 YS rate of 46%–59%
IIIC	(T1-4bN1bM0); (T1-4bN2bM0); or ≥4 metastatic LNs, matted LNs, or in-transit met(s)/satellite(s) have a 5 YS rate of 24%–29%
IV	(M1a) has a 5 YS rate of 19%; (M1b) has a 5 YS rate of 7%; (M1c) has a 5 YS rate of 10%

TREATMENT

- Management of squamous cell and adenocarcinomas has been wide radical excision (radical hemi/vulvectomy) with a 1-cm to 2-cm gross margin with groin (S)LND. For lesions that invade less than a depth of 1 mm, the groin LND can be omitted. If the lesion is lateral (more than 2 cm from the midline), dissection of the contralateral groin can be omitted. If the lesion is midline, or within 2 cm of a midline structure, a bilateral groin SLND should be performed.

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- Early stage T1 and ≤ 4 cm T2 lesions:
  - Less than 1 mm DOI: wide local resection
  - Greater than 1 mm DOI: radical local resection or modified radical vulvectomy with groin SLND
- Larger T2 and T3 lesions: obtain radiology imaging to evaluate LN status.
  - If radiologically negative:
    - Can offer EBXRT to primary tumor/groins/pelvis with concurrent platinum-based chemotherapy *or*
    - Perform complete groin LND:
      - If positive LN: EBXRT to primary tumor/groins/pelvis with concurrent platinum-based chemotherapy
      - If negative: EBXRT to primary tumor and selective EBXRT to groin LN with concurrent platinum-based chemotherapy.

      After completion of neoadjuvant chemoradiation: biopsy of the tumor bed to confirm complete pathologic response is indicated, or resection of residual tumor with wide surgical margins is appropriate. If pathologic margins are still positive, consider re-resection, additional EBXRT, and/or chemotherapy. If unresectable, additional EBXRT can be considered, and/or systemic therapy, or best supportive care.
    - If bulky inguinofemoral LN are present with an unresectable T3 lesion:
      - Resection of the bulky LN before commencement of chemoradiation can be performed *or*
      - Chemoradiation alone can be performed.
    - For T4a lesions:
      - Radical vulvectomy with bilateral groin LND or a pelvic exenteration can be considered.
      - Neoadjuvant combination chemotherapy and XRT ± LND.
    - Metastatic disease beyond the pelvis: any T, any N, M1
      - EBXRT for locoregional control and/or chemotherapy for control and symptom palliation, or best supportive care.
    - Management of a positive SLN:
      - EBXRT with concurrent cisplatin chemotherapy to the bilateral groins and whole pelvis (WP)
      - Complete bilateral inguinofemoral LND:
    - Management of positive LN from complete inguinofemoral LND: adjuvant XRT and cisplatin chemotherapy if:
      - Greater than 2 LN are positive
      - Greater than 1 LN is positive with greater than 2-mm sized metastasis *or*
      - Extracapsular LN involvement is present.
    - Neoadjuvant combination chemotherapy and XRT is considered as upfront therapy in larger T2 lesions, as well as T3 and T4 lesions. These patients can be treated with 50.4 Gy groin and WP-XRT with concurrent cisplatin at 40 to 50 mg/m^2 weekly. A groin LND/SLND can be performed before XRT, and if negative WP XRT can be omitted and XRT fields tailored to the primary tumor including potential en face therapy. Posttreatment surgical evalu-

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ation with resection of residual tumor and/or groin LND should be performed.
    - Fixed or ulcerated LN can be surgically resected with XRT to follow; or if unresectable, preoperative chemoradiation with postoperative resection of any macroscopic residual disease.
- The femoral triangle is anatomically bordered by the inguinal ligament superiorly, the sartorius muscle laterally, and the adductor longus muscle medially. The incision site for the groin LND starts 2 cm below a line drawn between the ASIS and the pubic tubercle. The skin flap is preserved. The upper flap is dissected toward the inguinal ligament. The LN-bearing tissue, which is attached to the inguinal ligament, is removed, and the superficial epigastric and superficial circumflex vessels should be ligated. The lower flap is then dissected. The saphenous vein, which runs through the medial aspect of the triangle, should be conserved, and its tributaries ligated.
- If an **ipsilateral groin LN** is found to be positive at final pathology for a unilateral tumor, management of the contralateral groin should be considered. Options include dissection of the contralateral groin, adjuvant bilateral groin and pelvic XRT, or a combination of contralateral groin LND and if negative, unilateral groin/pelvic XRT.
- The risk of contralateral positive LN with a negative ipsilateral groin LND is between 0.4% and 2.6%. GOG 74 demonstrated a 2.4% risk of isolated contralateral positive LNs in tumors 2 cm or less in size. If the DOI was less than 5 mm, contralateral LN metastasis occurred in 1.2% (4). Contralateral positive LNs have been found in 0.9% of patients if the tumor was less than 2-cm wide (5). In another study, a 1.8% rate of positive contralateral LNs was demonstrated if the ipsilateral groin LNs were found to be negative. In no patients were contralateral positive groin LNs found if the tumor was less than 2-cm wide and invasion was less than 5 mm (6).
- Sentinel groin LND can potentially decrease the extent and complication rate of the groin LND. The combined sequenced injection of Technetium-99m (^{99m}Tc) radiolabeled albumin and blue dye to the primary tumor, followed by intraoperative scintillation, has proven sensitive and specific enough for sentinel node identification. If frozen section is positive for LN metastasis, a complete bilateral groin LND should be performed. Radiation without completion LND is under investigation. Indications for performing a SLND are:
    - Negative clinical groin examination and imaging
    - Primary unifocal tumor
    - Tumor size less than 4 cm
    - No prior vulvar surgery to have altered lymphatic flow
- There is a relationship between margin status and recurrence. Heaps et al (7) reported on margin status: if there is less than 8 mm of fixed tumor-free tissue at resection, 13 of 23 patients recurred locally, whereas if the margins were greater than 8 mm, only 8 of 112 patients recurred. Thus, for positive or close margins, re-excision, and/or adjuvant XRT to the vulva can decrease the local recurrence rate. Those treated with adjuvant XRT had a 44% recurrence rate versus those observed who had a 75% recurrent rate (8). Tumor thickness greater than 5 mm, tumor >4 cm in size or LVSI, may also be indications for adjuvant local XRT.
- Adjuvant groin and WP-XRT is indicated for FIGO stages 3B, 3C, and 4A. Concurrent radiosensitizing cisplatin chemotherapy should be considered.

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- There are complications of a radical vulvectomy and groin LND. The wound infection rate is 29%. The wound breakdown rate is 38% for triple incision surgery versus 68% for en bloc resection. Lymphedema occurs at a rate of 7% to 19%. Lymphocytes occur at a rate of 7% to 28%. Cellulitis or lymphangitis can occur due to *beta Streptococcus*. Prophylactic antibiotics are warranted in patients with chronic lymphedema and if prone to cellulitis. Nerve injuries or paresthesias can also occur.
- Basal cell carcinomas are rarely metastatic. Treatment is with excisional biopsy to include a minimum margin of 1 cm and no LND.
- Verrucous carcinoma is a low grade tumor that is locally invasive and rarely metastasizes. Treatment is wide radical excision. Radiation therapy is commonly avoided due to concerns about aggressive transformation and metastasis.
- Vulvar sarcomas are also treated with wide radical excision. Combination chemotherapy and XRT may assist in disease management.
- Vulvar melanoma patients should undergo a wide radical excision with bilateral groin SLND.
  - There are data to suggest that radical surgery versus wide local excision yields no difference in overall survival (OS) (9).
  - LND in vulvar melanoma is of prognostic indication only; it is not therapeutic. Removal of enlarged nodes is adequate treatment.
  - Margins: the surgically desired margin for in situ disease is 0.5 mm; for a 1-mm thick tumor, a 1-cm margin; for 1.01- to 2-mm thick lesions, a 1- to 2-cm margin; for 2.01- to 4-mm thick lesions, a 2-cm margin; and for a lesion greater than 4-mm thick, a 2-cm margin.
  - Most failures are distant.
  - AJCC stage is the most important prognostic factor.
  - Adjuvant therapy for vulvar melanoma can be single-agent chemotherapy including dacarbazine, temozolomide, cisplatin, vinblastine, or paclitaxel. Combination chemotherapy can consist of cisplatin and paclitaxel.
  - Biological agents can be used with standard cytotoxic drugs or alone. Biologicals include ipilimumab, alpha-interferon, and vemurafenib.
- Paget's disease:
  - For noncutaneous vulvar Paget's disease, there is no benefit to an extensive resection or deep vulvectomy.
  - Treatment: for cutaneous vulvar Paget's, surgical resection is the mainstay. Other treatments are:
    - Surgery: a simple wide resection is recommended, with a 1-cm clinically negative margin. Response rates range from 33% to 70%. The risk of recurrence is high at 58% overall. If margins are negative the risk is 18% to 38% and if positive range between 45% and 61%. Frozen section of the margins has not been found to be better than visual inspection (false-negative rate 35%–38%). Permanent section margin status also did not predict recurrence: with 33% recurrence if negative margins versus 40% recurrence if positive margins (10).
    - Radiation therapy: response rate of 62% to 100% with a recurrence rate of 0% to 35%.
    - **Topical** chemotherapy with bleomycin or 5FU: response rate of 57% to 100%, with a recurrence rate of 25%. Adverse events: pain, moist desquamation, allergic reactions.

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- Photodynamic therapy: 5-aminolevulinic acid with light wavelengths. Response rate of 14% to 50%, with a recurrence rate of 38% to 56%.
- Laser therapy: response rate of 53% to 75% with a recurrence rate of 67%.
- Imiquimod: response rate 52% to 80%, recurrence rate 19%.

RECURRENCE

- The risk for local recurrence is close surgical margins. There are data to support that an 8-mm fixed margin (a 1-cm fresh margin) is adequate to diminish local recurrence from 50% if margins were less than 8 mm, to 0% if margins were greater than 8 mm. Surgical margins of 2 cm are still recommended, but if anatomy does not permit (urethral, anal, or vaginal margins that would significantly compromise function), a 1-cm margin can be adequate (7). Farias-Eisner et al (11) looked at radical local excision and LND for stages I and II vulvar cancers, and found that radical local excision had the same survival as those treated more radically with vulvectomy, and LN status had the largest impact on survival (98% OS if negative nodes were identified vs. 45% if positive nodes were found).
- For local recurrence, a radical excision should be performed with complete bilateral groin LND if not done previously. If groin LN were previously irradiated and clinically negative at the time of recurrence, resection of vulvar recurrence alone is recommended. If margins are negative, observation or additional XRT can be considered. If margins are positive and LN is negative, re-excision or EBXRT with or without brachytherapy XRT ± chemotherapy can be considered. If margins are negative and LN is positive, then concurrent chemoradiation should be offered, and if margins are positive and LN is positive, EBXRT with/without brachytherapy and concurrent chemotherapy ± re-excision should be considered. If radical re-excision is contraindicated or declined, EBXRT with or without brachytherapy and concurrent chemotherapy is recommended. This can be followed by surgical resection of residual tumor if present.
- Isolated perineal recurrences can be cured 75% of the time with salvage surgery. If the recurrence is central and regional, a pelvic exenteration can be considered.
- If groin nodal recurrence is detected: resection of the involved LN or a complete LND can be performed, followed by concurrent chemoradiation, if not previously performed. If the groin recurrence is fixed or large, then concurrent chemoradiation should be offered.
- If there is an isolated pelvic nodal recurrence: resection can be considered, and/or concurrent chemoradiation should be offered to follow.
- If distant metastases are identified on comprehensive workup, palliative chemotherapy and/or EBXRT should be considered.
- For LN recurrence in melanoma, pathology should be confirmed via biopsy, and imaging should also be obtained with PET/CT or CT of the chest/abdomen/pelvis. If the LN recurrence is in the groin, the entire LN basin should be dissected if not previously performed, and the enlarged LN should be resected. If a prior LND was performed, removal of the node itself is adequate. If the disease is completely resected, XRT, alpha interferon, and/or a clinical trial can be offered. If the disease is unresectable, systemic therapy, XRT, or a clinical trial can be offered. If there are clinically positive superficial LNs or there are three or greater positive LNs, iliac and obturator LND should be considered.

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SURVIVAL

The 2Y survival (YS) for nonmelanoma vulvar cancer patients with positive groin LN is 68%, and for those with positive pelvic LN is 23% (Table 2.29).

FOLLOW-UP

- Every 3 months for the first 2 years
- Every 6 months for the next 3 years
- Annual visits thereafter

NOTABLE TRIALS

- GOG 36: this surgical pathology study evaluated 637 patients with vulvar cancer, all of whom had tumors of less than 5 mm DOI. Risk factors for local recurrence and LN metastasis were studied. Multivariate risk factors that were predictive of groin LN metastasis were: tumor size less than 2 cm (18.9% + LN); greater than 2 cm (41.6% + LN). Independent predictors of groin LN metastasis were: tumor grade, LVSI, depth of invasion, age, and fixed or ulcerated LN. A clinically negative groin examination had a false-negative rate of 23.9%. Those patients in GOG 36 who were identified with positive groin LNs were randomized to GOG 37 (12,13).
- GOG 37: this study identified 114 patients with positive groin LNs after a radical vulvectomy and bilateral groin LND, and randomized them to an ipsilateral pelvic LND or to groin and pelvic XRT. The XRT was dosed at 45 to 50 Gy. 5% recurred in the XRT group, and 24% recurred in the pelvic LND group. The 2 YS was 68% for those treated with groin and pelvic XRT versus 54% for those who received the pelvic LND. The number of positive LNs influenced survival: one positive LN yielded an 80% OS, whereas 4 or more positive LNs had a 27% OS. The incidence of positive pelvic LNs if groin LNs were positive was 28%. There was a 9% incidence of local vulvar recurrence in both arms. A follow-up analysis was performed (15): the 6 YS for patients who received XRT was 61% versus 41% for those who received the pelvic LND. The 6 YS for cancer-related deaths was 51% versus 29% for the pelvic XRT versus pelvic LND groups, respectively (HR, 50.49). Poor prognostic factors were: clinically suspicious or fixed LNs, or greater than two positive groin LNs. A ratio of 20% positive LNs to total LNs was associated with contralateral metastasis, relapse, and cancer-related death, thus the cutoff for recommending XRT. 44% of patients in the XRT arm died secondary to other causes. The actual 3Y disease specific death rate was 25% (14).

Table 2.29 Vulvar Cancer 5 YS by Stage

Stage	5 YS (%)
I	95
II	75–85
III	55
IVA	20
IVB	5

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- GOG 74: this study surgically evaluated the outcomes of 143 patients with early stage vulvar tumors who underwent a superficial groin LND with a modified radical vulvectomy. Overall, 7% developed isolated groin recurrences, and of those with a groin recurrence, 91.7% died. The median time to recurrence in the vulva was 35.9 months, and 7 months for recurrence in the groin. The median survival time after recurrence was 52.4 months for vulvar recurrence and 9.4 months for groin recurrence. This study is criticized for a high number of grade 3 tumors (28%) and that of the nine groin recurrences, three were in an undissected groin (patients who refused groin dissection) (4,16).
- GOG 88: because patients in GOG 37 with positive groin LNs had favorable outcomes with XRT the question as to whether a groin LND was necessary if prophylactic XRT was administered was investigated. This study evaluated 50 patients after a radical vulvectomy and randomized them to prophylactic groin XRT or to groin LND. In this study, 0 out of 25 patients recurred if a LND was performed, followed by XRT for positive LN (of which 20% were indeed positive), versus an 18.5% recurrence if prophylactic groin XRT was administered to an undissected groin with, therefore, an unknown LN status. Criticisms of this study were: underdosing of the groins as the dose prescription point was to 3 cm and on review, the average vessel depth was 6.1 cm (range 2–18.6 cm) with an average BMI of 25.6 (17,18).
- GOG 101: this phase II study evaluated 73 patients with T3 or T4 disease treated with neoadjuvant chemotherapy and XRT. The XRT total dose was 47.6 Gy administered in 1.7 Gy fractions as a hyper-fractionated split dose regimen of 23.8 Gy BID for 4 days and daily for 6 days with a 2-week break, with two concurrent cycles of cisplatin 50 mg/m^2 day 1 and 5-FU 1,000 mg/m^2 days 1 to 4 given week 1 of each course of XRT. 69 of 71 women were converted to a resectable status, with 68 patients keeping urinary and fecal capacity. 47% (33 of 71) had a CCR and 70% of these were CPR. 2.8% remained unresectable. There was a 55% OS. A companion study to GOG 101 was done for patients with unresectable positive groin LNs (N2/3 nodes); 38 of 40 patients became resectable, with 15 of 37 patients having a CPR. Overall, 29 of 38 patients had local control of their disease. 19 patients recurred: 9 locally and 8 distant (19,20).
- GOG 205: this phase II study evaluated 58 patients with T3 or T4 disease treated with neoadjuvant chemotherapy and XRT. XRT was dosed at 57.6 Gy with concurrent weekly cisplatin dosed at 40 mg/m^2. Surgical resection followed for residual tumor (or biopsy to confirm CCR). 64% of patients had a CCR (37 of 58) and 78% of these had a CPR. In this study, there was no hyper-fractionation, no mid-treatment break, and no 5-FU. Management of the groin LNs in these studies was standardized. Clinically negative or resectable groin LNs underwent groin LND before neoadjuvant therapy. If there were unresectable groin LNs, the groin dissection was performed after neoadjuvant therapy (21).
- GOG 173: in this study, 452 eligible patients with a tumor size ≥2 cm, ≤6 cm, and with at least 1-mm invasion underwent radical vulvectomy with groin lymphatic mapping. 772 groin dissections were performed. A sentinel LN (SLN) was identified in 418 of 452 patients. LN metastases were found in 132 of 418 patients (31.6%). The SLN was positive in 121 of 418 patients. 11 (8.3%) patients with a negative SLN were found to have positive LNs identified on final

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complete dissection pathology (thus 132 total SLN positive patients). 23% of the true-positive patients were detected by immunohistochemistry (IHC) analysis of the SLN. The sensitivity of SLN dissection was 91.7% and the FNPV was 3.7% (90% upper confidence bound = 6.1%). In patients with tumors less than 4 cm, the false-negative rate was 2% (22).

- GOG 195: 137 patients were evaluable for analysis of lymphedema after randomization to receive sutured closure versus fibrin sealant applied in the wound followed by sutured closure. The incidence of grade 2/3 lymphedema was 67% in the sutured closure arm and 60% in the fibrin sealant arm; thus no benefit to fibrin sealant was found. The incidence of lymphedema was correlated strongly with inguinal infection and not increased in those who received adjuvant XRT (23).
- DiSaia et al recommended omitting the deep LND to decrease morbidity without compromising survival. 50 stage I patients with negative superficial nodes were retrospectively reviewed. No deep LND was performed. There were no recurrences after 12 months (24).
- GROINSS-V-1/GOG 270 **GRO**ningen **IN**ternational **S**tudy on **S**entinel nodes in **V**ulvar cancer: this study evaluated 403 patients. 623 groin dissections were performed. All tumors were greater than 1 mm DOI, unifocal, squamous, and less than 4 cm in size with clinically negative groin LN. A radical vulvectomy and sentinel groin LND were performed in all patients. Follow-up was 35 months. A combination of radioactive tracer and blue dye was used. 67% had negative SLN, 32.9% had a positive SLN. Of 259 patients with unifocal vulvar disease and a negative sentinel node (median follow-up time, 35 months), 6 had groin recurrences diagnosed, for a false-negative rate of 2.3%. The 3 YS rate was 97%. The 3Y DSS rate for patients with SLN metastasis greater than 2 mm was 69.5%, the 3Y DSS of the SLN metastasis less than 2 mm was 94.4%. The short-term morbidity was decreased in the SLN patients compared with those patients with a positive sentinel node who underwent a complete inguinofemoral lymphadenectomy. Wound breakdown in the groin was 11.7% versus 34.0%, and cellulitis occurred at 4.5% versus 21.3%. The long-term morbidity was also less with recurrent erysipelas occurring at a rate of 0.4% versus 16.2%, and lymphedema of the legs seen in 1.9% versus 25.2% of patients. GROINSS-V-I 10Y follow-up: the median follow-up was 105 months. The overall recurrence rate was 37.2% at 5 years, at a median time of 27 months. The local recurrence rate was 27.2% at 5Y and 39.5% at 10Y after primary treatment. The primary isolated groin recurrence rate was 4.1% and distant recurrence was 2%. In SLN– patients, the isolated groin recurrence was 2.5%. The local recurrence rate for SLN– patients was 24.6% at 5Y and 36.4% at 10Y. In SLN+ patients, the groin recurrence was 8% and distant recurrence 6.8% at 5 and 10Y. Local recurrence was 33.2% at 5Y and 46.4% at 10Y. SLN– patients had 5 and 10Y DSS of 93.5% and 90.8% compared to SLN+ patients of 75.5% and 64.5%. For all patients, 10Y DSS decreased from 90.4% to 68.7% for local recurrence. For SLN– patients, 10Y DSS decreased from 96.1% to 80.8%, and SLN+ patients, 10Y DSS decreased from 77.7% to 44.6% for local recurrence (25,26).
- **GRO**ningen **IN**ternational **S**tudy on **S**entinel nodes in **V**ulvar cancer (GROINSS-V) **II** NCT01500512: eligible patients undergo planned radical vulvectomy and sentinel LND. These are patients with unifocal tumors less than 4 cm in size and less than

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N3 disease. Patients without pathologic LN involvement undergo observation. Patients with less than 2 mm LN involvement undergo XRT. Patients with significant LN involvement undergo inguinofemoral lymphadenectomy and XRT with or without chemotherapy according to institutional guidelines. Results pending.

- AGO-CaRE-1 (**C**hemo **a**nd **R**adiotherapy in **E**pithelial Vulvar Cancer): this was a retrospective multicenter cohort study in Germany, from 1998 to 2008 reviewing 1,618 documented patients with primary squamous-cell vulvar cancer stage IB and higher. Of the patients, 1,249 had surgical groin staging and known LN status and were further analyzed. Of the 1,249 patients, 447 (35.8%) had LN metastases (N+). The majority of N+ patients had one (172 [38.5%]) or two (102 [22.8%]) positive nodes. The 3Y PFS of N+ patients was 35.2%, and the OS was 56.2% compared with 75.2% and 90.2% in node-negative patients (N–). 244 (54.6%) N+ patients had adjuvant therapy, of which 183 (40.9%) had XRT directed at the groins (± other fields). 3Y PFS and OS rates in these patients were better compared with N+ patients without adjuvant treatment (PFS: 39.6% vs. 25.9%, hazard ratio [HR] 0.67; 95% confidence interval [CI]: 0.51–0.88; $p = 0.004$; OS: 57.7% vs. 51.4%; HR 0.79; 95% CI: 0.56 to 1.11; $p = 0.17$). This effect was statistically significant in multivariable analysis adjusted for age, ECOG PS, FIGO stage, grade, invasion depth, and number of positive nodes (PFS: HR 0.58; 95% CI: 0.43–0.78; $p < 0.001$; OS: HR 0.63; 95% CI: 0.43–0.91; $p = 0.01$). Thus, adjuvant XRT was associated with improved prognosis in node-positive patients; however, outcomes after adjuvant XRT remains poor compared with node-negative patients. Adjuvant chemoradiation should improve therapy beyond XRT alone (27).
- Impact of adjuvant chemotherapy in addition to XRT for node-positive vulvar cancer: a National Cancer Data Base (NCDB) analysis. A total of 1,792 patients were reviewed: 26.3% received adjuvant chemotherapy in addition to XRT, and 76.6% had one to three involved LN. The median unadjusted survival with and without adjuvant chemotherapy was 29.7 and 44 months, $p = 0.001$. Delivery of adjuvant chemotherapy resulted in a 38% reduction in the risk of death (HR 0.62; 95% CI: 0.48–0.79; $p < 0.001$) for node positive vulvar cancer patients in the NCDB. A propensity adjusted analysis was performed and able to show a significant improvement in 3Y OS of 53.9% versus 46.9% in patients receiving chemoradiation (28).
- GOG 279: this is a phase II trial of approximately 52 patients evaluating cisplatin and gemcitabine concurrent with IMRT for the treatment of locally advanced squamous cell carcinoma of the vulva. Eligible patients are T2 to T3, N0 to N3 squamous cell cancers not amenable to primary surgical resection. Pre-treatment SLND or groin dissection is performed. Patients will be treated with 64 Gy IMRT total dose to the vulva and 50 Gy to the nonmalignant groin or 60 Gy to involved LN (>3 +LN, extracapsular involvement, or close margins), concordant with gemcitabine 50 mg/m^2 and cisplatin 40 mg/m^2 weekly during XRT. Surgical resection of residual disease is scheduled at 6 to 8 weeks post-therapy. Results are pending.
- Debulking of clinically involved LN followed by XRT (compared to complete groin LND or SLND followed by XRT for node positive disease) had fewer complications. There was no increase in groin recurrences or changes in OS in 68 patients (29).

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- Vemurafenib is an antibody against the *BRAF* receptor. The V600E mutation occurs in some melanomas and constitutively activates the *BRAF* gene. In a randomized trial of 675 untreated metastatic melanoma patients stage IIIc or IV who were *BRAF* V600E positive, vemurafenib was compared to dacarbazine. Vemurafenib was dosed at 960 mg orally twice daily and dacarbazine at 1,000 mg/m^2 IV every 3 weeks. The 6-month OS was 84% in the vemurafenib group and 64% in the dacarbazine group. Response rates were 48% for vemurafenib and 5% for dacarbazine (30).
- RTM-0905: a phase II trial of dasatinib 70 mg PO BID in c-KIT-positive patients with unresectable locally advanced or stage IV mucosal, sacral, and vulvovaginal melanoma. Results pending.

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Vaginal Cancer

CHARACTERISTICS

- Vaginal cancer represents 1% to 2% of all female genital tract malignancies. The median age at diagnosis is 60 years. Most vaginal cancers are metastatic lesions from other sites, including the cervix, uterus, breast, gestational trophoblastic disease, and the gastrointestinal (GI) tract. Primary vaginal cancers are commonly found in the upper one third of the vagina, often in the posterior fornix. There are 4,810 new cases with 1,240 deaths estimated for 2017.
- Symptoms include vaginal discharge, vaginal bleeding, tenesmus, pelvic pain, bladder irritation, and pelvic fullness.
- If the patient has a history of uterine, cervical, or vulvar cancer, the vaginal lesion is considered a recurrent cancer unless proven otherwise by discriminating pathology or greater than 5 years have intervally passed since prior diagnosis.
- Risk factors for vaginal cancer include human papillomavirus (HPV) infection, chronic vaginal irritation, prior treatment for cervical cancer, prior CIN, and a history of in-utero exposure to DES.
- DES was used from 1940 to 1971. Vaginal adenosis and vaginal adenocarcinoma are characteristics of exposure. Other physical representations are a cockscomb cervix. The risk of clear cell carcinoma is 1:1,000 with a history of DES. The peak age at diagnosis was 19 years. Surveillance for women who were exposed to DES in utero includes at least yearly gynecologic exams with cervicovaginal cytology (and colposcopy as indicated) to occur indefinitely.
- The route of spread is direct, lymphatic, or hematogenous. The route of lymphatic spread depends on the location of the lesion. If the lesion is in the upper two thirds of the vagina, metastasis is often directly to the pelvic lymph nodes (LNs). If the lesion is in the lower one third of the vagina, metastasis can often be to the inguinal-femoral LNs, and/or to pelvic lymph nodes. Hematogenous spread often occurs late in the disease process.
- The most important prognostic factor is stage of disease. Age is also an important factor. Melanomas and sarcomas have the worst prognosis. Lesions of the distal vagina tend to have a worse prognosis than proximal lesions. Size less than 3 cm has a better prognosis than if larger than 5 cm. LN status also confers prognosis, with a 5-year survival (YS) of 33% for positive LNs compared to 56% for negative LNs.

PRE-TREATMENT WORKUP

The pre-treatment workup is colposcopy of the entire genital tract and physical examination. Diagnosis is via biopsy often guided with colposcopy. It may be necessary to perform an examination under anesthesia with cystoscopy and

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proctoscopy. These procedures may also help with initial staging. Chest x-ray, intravenous pyelography (IVP), cystoscopy, proctoscopy, and barium enema are FIGO-approved diagnostic studies. CT, MRI, and PET imaging may assist in evaluating extent of disease and aid in treatment planning.

HISTOLOGY

- 80% of vaginal cancers are of squamous cell histology.
- 5% to 9% are adenocarcinomas.
- Malignant melanoma represents 2.8% to 5% of vaginal neoplasms. Vaginal melanomas are more often found in the lower one third of the vagina.
- Rhabdomyosarcoma is usually found as the botryoid variant of embryonal rhabdomyosarcoma and is the most common malignant tumor of the vagina in infants and children; 90% of patients are younger than 5 years. On clinical examination, grape-like edematous masses may protrude from the vagina. The histologic pearl is the presence of a cambium layer beneath an intact vaginal epithelium.
- Leiomyosarcoma can also be found, and this can occur in women with a prior history of radiation therapy (XRT).

STAGING

Staging continues to be clinical, closely following cervical cancer parameters (Tables 2.30A–D).

Table 2.30A AJCC 8th Edition: T Category

T	FIGO stage	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the vagina
T1a	I	Tumor confined to the vagina, measuring ≤2.0 cm
T1b	I	Tumor confined to the vagina, measuring >2.0 cm
T2	II	Tumor invading paravaginal tissues but not to pelvic sidewall
T2a	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring ≤2.0 cm
T2b	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring >2.0 cm
T3	III	Tumor extending to the pelvic sidewall and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

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Table 2.30B AJCC 8th Edition: N Category

N	FIGO stage	N criteria
NX		Regional LNs cannot be assessed
N0		No regional LN metastasis
N0(i+)		Isolated tumor cells in regional LN(s) not greater than 0.2 mm
N1	III	Pelvic or inguinal LN metastasis

LN, lymph node.

Table 2.30C AJCC 8th Edition: M Category

M	FIGO stage	M criteria
M0		No distant metastasis
M1	IVB	Distant metastasis

Table 2.30D AJCC 8th Edition: Stage Grouping

When T is	And N is	And M is	Then the stage group is
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1–3	N1	M0	III
T3	N0	M0	III
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

If there is clinical involvement of the cervix or the vulva, the tumor should be classified as a primary cervical or vulvar cancer, respectively; tumors limited to the urethra should be classified as urethral cancers.

TREATMENT

Treatment depends on the location and depth of the lesion, the stage of the cancer, and medical comorbidities.

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- Treatment for stage I squamous cell or adenocarcinomas that involve the upper two thirds of the vagina can include a radical hysterectomy with upper vaginectomy and LND, or an upper vaginectomy and parametrectomy with LND if the uterus has previously been removed. XRT without surgery has equivalent outcomes. Concurrent platinum-based chemotherapy has been adopted to follow cervical cancer guidelines. If the lower one third of the vagina is involved, external beam radiation therapy (EBXRT) fields should include the groins. Dosing is 50.4 Gy EBXRT to a total of 80 to 85 Gy with interstitial or Fletcher-Suit brachytherapy.
- Treatment for stages II, III, and IV is definitive XRT with concurrent platinum-based chemotherapy. If the lesion size is 2 cm or greater, surgical resection can be considered to potentially optimize XRT. XRT usually includes EBXRT and intracavitary or interstitial therapy to a total dose of 85 to 90 Gy. If the lower one third of the vagina is involved, the groins should also be irradiated.
- Treatment for melanoma is radical surgical resection if possible. Exenterative surgery has not been found to provide additional survival benefit. Chemotherapy with biologic therapy may provide adjuvant benefits.
- The treatment of rhabdomyosarcoma is usually multimodal with therapy consisting of surgical resection, XRT, and systemic chemotherapy. Commonly used agents are vincristine, actinomycin, and cyclophosphamide. Another regimen is cyclophosphamide, doxorubicin, and dacarbazine.
- Leiomyosarcoma is treated with radical surgical resection and the consideration of adjuvant XRT and/or chemotherapy.

RECURRENT DISEASE

If recurrent disease is identified, a full metastatic workup should be employed. If only local disease is confirmed, a wide local excision or a partial (radical) vaginectomy can be performed. If central disease is identified, a pelvic exenteration can be considered. If there is distant metastasis, chemotherapy with or without XRT can be considered (Table 2.31).

SURVIVAL

Table 2.31 Vaginal Cancer 5Y Survival by Stage

Stage	5 YS (%)
I	84
II	75
III	57
IV	10

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FOLLOW-UP

- Physical and pelvic examinations are recommended: a Pap smear may help with detection of recurrence but at most annually.
  - Every 3 months for the first 2 years
  - Every 6 months for the next 3 years
  - Annual examinations thereafter

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Gestational Trophoblastic Disease

CHARACTERISTICS

- Gestational trophoblastic disease (GTD) describes a group of tumors that arise from trophoblastic cells. This is usually the result of an abnormal fertilization event and includes molar pregnancy, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epitheliod trophobblastic tumor (ETT).
- Hydatidiform molar pregnancy occurs in approximately 1 out of 1,000 pregnancies in North America. Clinical features of a mole are vaginal bleeding in the first trimester or early second trimester; uterine size large for dates; ovarian theca-lutein cysts (seen in 46% of patients, 2% of which may torse); early preeclampsia less than 20 weeks (12%–17%); hyperthyroidism due to the similarity between the alpha subunit of both human chorionic gonadotropin (hCG) and thyroid-stimulating hormone (TSH) hormones; hyperemesis gravidarum (20%); passage of vesicles per vagina; and respiratory complaints due to tumor emboli or increased progesterone (27%).
- Risk factors for a molar pregnancy include age (<20 years or >40 years of age), history of a prior mole, and Asian ethnicity.
- WHO has classified GTD into two states: premalignant and malignant. The premalignant tumors are the complete and the partial moles. The malignant tumors are the invasive mole, gestational choriocarcinoma, ETT and PSTT. Within the malignant tumors are the categories of nonmetastatic and metastatic. Within the metastatic category are low-risk metastatic and high-risk metastatic disease.
- There is an increased risk for a second mole after a first molar pregnancy. This is usually paternally related. The risk of another molar pregnancy increases from 1 out of 1,000 to 1 out of 100. There is a familial recurrent hydatidiform mole syndrome (FRHM). This is an autosomal recessive disorder with mutations in NLRP7 (in 70% of cases) or KHDC3L (5% of cases) that results in a diploid complete mole of biparental origin.
- A mole and fetus have been diagnosed at a rate of 1 out of 100,000 pregnancies. There are data to suggest a 40% chance of a live birth. Persistent GTD is diagnosed in 55% of these patients, and 22.7% are found to have metastatic disease. There is an increased risk for hemorrhage, preeclampsia, and metastatic disease. The pregnancy should be terminated if these life-threatening complications occur.
- Tumors from other primary sites can produce hCG. Genetic studies should be performed on patient's tumors who are refractory to common first line and salvage therapies to rule out nongestational choriocarcinoma.

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HISTOLOGY

- Complete and partial moles are usually diagnosed at the time of uterine evacuation. Histopathology is the main diagnostic method. Other abnormal pregnancies/fetuses can be mistaken for a partial mole. These include Turner's, Beckwith-Wiedemann, and Edward's syndromes.
- A complete mole has no fetal components. Furthermore, the placental villi are hydropic (or edematous) with no identifiable vasculature. The origin of this mole is considered to arise from fertilization of an anuclear oocyte with either two sperm or one sperm that duplicates itself, thus all nuclear DNA is paternal (most commonly diploid with a 46XX karyotype) while the mitochondrial DNA is maternal. Fluorescence in situ hybridization (FISH) can confirm the diagnosis. The rate of persistent GTD after a complete mole is 15% to 20%.
- The partial mole's origin is thought to arise from the dual fertilization of an egg by two sperm, or duplication of a paternal chromosome resulting in triploidy with 2:1 paternal to maternal DNA content. Fetal components can be seen, along with fetal vasculature and hydropic villi. FISH can aid with the diagnosis if necessary, and immunohistochemistry can add information with positive staining for p57 KIP2. Cytogenetic techniques, to include chromosomal banding and restriction fragment length polymorphism (RFLP) analysis of DNA, have allowed chromosomal patterns for partial and complete molar pregnancies differentiation. The rate of persistent GTD after partial mole is 0.5% to 5% (Table 2.32).
- Choriocarcinoma occurs in 1 of 20,000 pregnancies and is inherently a high-risk disease at diagnosis, regardless of metastasis. It should be treated aggressively. 50% of tumors follow a term gestation, 20% occur after molar gestations (both partial and complete), and 25% occur after a spontaneous or elective abortion. These tumors have diverse, nonspecific ploidies and are highly malignant. Both cytotrophoblasts and syncytiotrophoblasts are present, with syncytiotrophoblasts predominating, but there are no chorionic villi. Metastasis occurs frequently to the lung (80% with symptoms such as hemoptysis or dyspnea), vagina (30% with bleeding), brain (10% with focal neurologic deficits, headache, mass effect), and liver (10% pain, hemoperitoneum).

Table 2.32 Molar Pregnancy Classifications With Characteristics

Characteristic	Complete mole	Partial mole
Hydatidiform edematous villi	Diffuse	Focal
Trophoblastic hyperplasia	Cyto- and syncytial	Syncytial
Embryo	Absent	Present
Villous capillary	No fetal RBC	Many fetal RBC
Gestational age at diagnosis	8–16 wk	10–22 wk
Beta hCG titer mIU/mL	>50,000 mIU/mL in 75%	<50,000 mIU/mL
Malignant potential	15%–25%	0.5%–5%
Karyotype	Diploid (46XX 95%, 46XY 5%)	Triploid (69XXY) 80%
Size for dates: Small Large	 33% 33%	 65% 10%

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- PSTT may follow a term gestation, a nonmolar abortion, a complete mole, and, in theory, a partial mole. These tumors are mostly diploid and produce very low amounts of beta hCG as well as serum human placental lactogen (HPL). This is due to the presence of intermediate cytotrophoblast cells. There is an increased proportion of free beta hCG. These tumors stain for HPL, B1-glycoprotein, and Ki-67. PSTT's grows slowly and can be seen years after any type of pregnancy. It can produce a nephrotic syndrome or hematuria. The prognosis depends on the time until diagnosis; if it presents less than 4 years since a pregnancy, the prognosis is better than if later. FIGO scoring is not used to determine treatment of PSTT. These tumor present with lung metastases in 10-29% of cases and 10% of patients develop metastases during followup. Treatment is recommended with hysterectomy and LND—ovarian conservation does not adversely affect outcomes. Adjuvant chemotherapy is recommended for: metastatic disease (also surgically remove primary tumor site) and for adverse prognostic factors such as interval from last known pregnancy greater than 2 years, deep myometrial invasion, tumor necrosis, mitotic count greater than 6/10 HPF. Recommended chemotherapy regimens are: EMA-EP or paclitaxel/cisplatin-paclitaxel/etoposide doublet.
- Quiescent GTD is the state of elevated beta hCG without documented hyperglycosylated hCG. There has never been a documented case of quiescent GTD with a beta hCG level that is higher than 230 mIU/mL. In this disease state, the residual mole lacks a cytotrophoblastic cell population. Therefore, there is no hyperglycosylated hCG production, and as a result, no invasion. Usually the residual mass of tissue dies after 6 months. In 10.4% of cases, however, quiescent GTD can activate and lead to persistent trophoblastic disease. Therefore, when a hyperglycosylated hCG is detected, the patient should be treated with chemotherapy. This is similar to a low malignant potential tumor. There are some data to suggest waiting to treat until a threshold beta hCG level of 3,000 mIU/mL is detected (1,2).
- Epithelioid trophoblastic tumor (ETT) is an extremely rare subtype derived from chorionic type intermediate trophoblast cells. Treatment is best with hysterectomy and LN dissection. Chemotherapy is recommended in addition to surgery for metastatic disease (after removal of the primary tumor site), and for adverse prognostic factors such as interval from last known pregnancy greater than 2 years, deep myometrial invasion, tumor necrosis, mitotic count greater than 6/10 HPF. EMA-EP or the paclitaxel/cisplatin-paclitaxel/etoposide doublet are chemotherapy options.

DIAGNOSIS

- Diagnosis of a mole is by ultrasound and serum beta hCG level. Invasive hydatidiform mole/GTD occurs usually after evacuation of a complete mole or partial mole.
- The diagnosis of an invasive mole/GTN is made if there is: persistent beta hCG for 6 months after evacuation of a molar pregnancy, an elevating beta hCG (a 10% rise over three values in 2 weeks), a plateauing beta hCG (a plateau of 10% over four values in 3 weeks), or evidence of metastatic disease (mainly lung). In addition, some may consider the presence of an hCG value greater than 20,000 mIU/mL 4 weeks after evacuation, diagnostic for an invasive mole. It is imperative to perform dual serum and urine hCG testing to rule out phantom hCG, which is due to heterophilic/cross-reacting antibodies in the serum hCG test.

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PRE-TREATMENT WORKUP

- The pre-treatment workup of GTD is a pelvic ultrasound (which can document the primary tumor as a uterine mass and give its dimensions) and a chest x-ray. If the chest x-ray is negative, a CT of the chest can be obtained. If the lungs show metastatic disease, it is then necessary to obtain an MRI of the abdomen and the brain. Alternatively, some practitioners routinely obtain a CT of the chest, abdomen, and pelvis for initial evaluation, but only the lesions seen on the CXR should be scored. A urine beta hCG and serum beta hCG both need to be performed to confirm beta hCG presence. Serum laboratories include a quantitative beta hCG and hyperglycosylated hCG, CBC, renal function tests, liver function tests, thyroid function tests, and a physical examination. A lumbar puncture can be considered if central neurologic symptoms are present and the brain MRI is negative. The plasma to CSF ratio of hCG can be less than 60 in cases with cerebral metastasis, but this ratio is not always reliable.
- Repeat D&C is controversial. With a second D&C, the risk of needing chemotherapy is 21%; with a third D&C, the risk of needing chemotherapy more than doubles to 47%, possibly due to hematogenic metastasis induced by curettage (3).

SERUM BETA hCG

- **Serum beta hCG** is a very sensitive and specific marker for trophoblastic tissue and thus a good tumor marker for this disease. The half-life of beta hCG is 24 to 36 hours. The amount of hCG correlates to the amount of viable tissue: 5 mIU/mL is approximately equal to 10,000 to 100,000 viable cells. However, it is also produced by many other carcinomas, including lung cancer, ovarian cancer, and colon cancer. Genetic testing should be performed on refractory tumors to ensure the primary is GTD and not otherwise.

STAGING

- FIGO 2002 staging is **clinical** incorporating WHO risk factors to obtain a final modified FIGO/WHO risk score (Table 2.33 A–C).

Table 2.33A AJCC 8th Edition: T Category

T	FIGO	T Criteria
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the uterus
T2	II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension

Table 2.33B AJCC 8th Edition: M Category

M	FIGO	M Criteria
M0		No distant metastasis
M1		Distant metastasis
M1a	III	Lung metastasis
M1b	IV	All other distant metastasis

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Table 2.33C AJCC 8th Edition: Stage Grouping

When T is	And M is	The stage is noted with risk factor score to follow:
T1	M0	I: (risk score__)
T2	M0	II: (risk score __)
Any T	M1a	III: (risk score__)
Any T	M1b	IV: (risk score __)

Source: From Amin MB, Edge SB. (2017). *AJCC Cancer Staging Manual* 8th Edition. Chicago, IL: American Joint Committee on Cancer. With permission.

- **Prognostic factors** required for staging: patients are classified into low-risk or high-risk categories of metastatic disease based on the WHO score as calculated in Table 2.33. The scores from eight risk factors are summed and incorporated into the FIGO stage, separated by a colon (e.g., stage III:8). If the score is less than seven, they are considered low risk. If the score is seven or greater, they are considered high risk. The modified WHO prognostic scoring system is not applicable to patients with PSTT or ETT (Tables 2.34 and 2.35).

Table 2.34 WHO Prognostic Scoring System for GTD as Modified by FIGO (2002)

Score	0	1	2	4
Age	≤39	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4–6	7–12	>12
Pre-treatment serum hCG level (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor size including uterus	<3 cm	3–5 cm	>5	
Site of metastasis	Lung	Spleen, kidney	GI	Brain, liver
Number of metastases	–	1–4	5–8	>8
Prior failed chemotherapy drugs	–	–	1	≥2

TREATMENT

- Molar pregnancy GTD:
  - Evacuation via suction D&C is the primary treatment. Some clinicians avoid sharp curettage due to the increased risk of uterine perforation and possible metastasis. If fertility is not desired, a hysterectomy with ovarian preservation can be the primary treatment of a molar pregnancy.
  - Medications such as Prostin have been shown to increase the need for chemotherapy due to hematogenous spread via contraction of the uterine arteries.

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Table 2.35 GTD Metastatic Site Rate

GTD metastatic sites	Percent
Lungs	80
Vagina	30
Pelvis	20
Brain	10
Liver	10
Bowel, kidney, spleen	5

Pitocin administered after cervical dilation can assist in uterine involution in addition to expression of uterine contents extracorporeally and not into the vascular system. RhoGAM should be given if the patient is Rh negative.

- Some patients with molar pregnancies are considered high risk for developing persistent or metastatic disease (Table 2.36). Chemoprophylaxis with a one-time dose of single-agent chemotherapy can be considered. In these patients, data have shown the rates of persistent disease have gone from about 50% to 15%. Chemoprophylaxis in lower-risk patients can also be considered if they are seen as potentially noncompliant.

- Invasive disease/GTN:
  - Stage I disease can be managed surgically or with chemotherapy.
    - Surgical management:
      - A hysterectomy with ovarian preservation can be performed if fertility is not desired. A single dose of either methotrexate or dactinomycin immediately prior to the surgical procedure can be considered for prophylaxis against embolism of tumor cells from surgical manipulation.
      - A second uterine curettage can be performed in low risk (Score 0–6) patients understanding that there is a high risk of uterine perforation. 38% of patients treated with a second D&C instead of single-agent chemotherapy normalized their hCG within 6 months, avoiding any chemotherapy; and 6.3% were re-catagorized histologically to have PSTT.
    - Single-agent chemotherapy is administered if hysterectomy is not performed. Chemotherapy is either with methotrexate or dactinomycin. The likelihood of success of weekly methotrexate is dependent on the WHO score. Weekly IM methotrexate is successful in 70% of patients with a WHO score of 0–1, but falls to 40% in those with a score of 2–4, and 12% in those who score 5–6. Biweekly pulsed dactinomycin showed a CRR of 44% when the WHO score was 5–6 (10).
  - Stage II disease follows the same chemotherapy principles as those of stage I disease.
  - Stage III disease is categorized as either low risk or high risk based on WHO risk scoring.
    - If the patient is considered low risk, initial single-agent chemotherapy is administered.
    - If the patient is high risk, combination chemotherapy with EMA-CO should be initiated.

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Table 2.36 GTD High-Risk Clinical Features for Metastatic Disease

Clinical feature	Percent risk of GTD
Delayed postmolar evacuation hemorrhage	75%
Theca lutein cysts >5 cm	60%
Acute pulmonary insufficiency following molar evacuation	58%
Uterus large for dates (16-wk size)	45%
Serum hCG >100,000 mIU/mL	45%
Second molar gestation	40%
Maternal age >40	25%

  - Stage IV disease is high risk, by definition, and is initially managed with combination chemotherapy. Treatment is usually with EMA-CO, but the methotrexate dose is increased to 1 g/m^2. If there are cerebral metastases, craniotomy to prevent herniation from mass or hemorrhage may be indicated. Consideration of intrathecal methotrexate or whole brain irradiation to 30 Gy is important. Intrathecal methotrexate is dosed at 12.5 mg, followed in 24 hours with 15–30 mg of oral folinic acid. This is given once with each course of CO during EMA-CO therapy.
- Single-agent chemotherapy is continued for two to three courses beyond normalization of the beta hCG for stages I to III. For high-risk and stage IV disease or a WHO score greater than 12, three to four additional courses are recommended after normalization of the beta hCG level. This is due to data suggesting that 100,000 viable cancer cells remain when the beta hCG becomes undetectable.
- Optimal therapy for PSTT is a hysterectomy with pelvic and para-aortic LN dissection. Ovarian preservation has not been found to be detrimental. This is a relatively chemoresistant tumor, so if the disease is found to be advanced, surgery with adjuvant chemotherapy is likely the best option. Chemotherapy can consist of EMA-EP or EMA-CO. The only prognostic factor identified regarding survival, is time from the last pregnancy. If this time is less than 4 years, patients usually do well; if it is greater than 4 years, this is usually universally fatal.
- ETT is generally more aggressive than PSTT but is treated in a similar fashion.
- Choriocarcinoma by definition is high-risk disease and should be treated with combination EMA-CO therapy.

MANAGEMENT OF ACUTE DISEASE-INDUCED COMPLICATIONS

- If there is uterine hemorrhage, vaginal packing, blood transfusion, and emergent uterine artery embolization can be performed. Laparotomy may be necessary for hysterectomy.
- Respiratory failure either from tumor embolization, pulmonary embolization, tumor burden, or hemorrhage may occur. Mechanical ventilation is contraindicated due to a high risk of trauma and iatrogenic hemorrhage,

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but continuous positive airway pressure (CPAP) is a good alternative. Risk factors for respiratory failure are as follows: 50% opacification of lung fields on CXR, dyspnea, anemia, cyanosis, and pulmonary hypertension. Consideration for those with a high thorax tumor burden, to decrease the risk of death from pulmonary hemorrhage or respiratory failure within the first 4 weeks of therapy, is to start with induction etoposide and cisplatin (EP) for one to two cycles, and continue thereafter with EMA-CO. Low-dose induction EP consists of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2 repeating weekly for one to two cycles before starting EMA-CO. High-risk patients receiving EP compared to patients not receiving EP had a higher, but not statistically significant, relapse rate (9% vs. 6% $p = 0.44$) and death rate (12% vs. 4%; $p = 0.88$) (4).

- If cerebral metastases are identified, vigilance for cerebral hemorrhage, edema, and herniation should be maintained. If a solitary lesion is found, site directed versus whole brain radiation therapy (WB-XRT) can be considered. If multiple lesions are identified, WB-XRT is recommended with dosing to 30 Gy in 200 cGy fractions. Premedication with 24 mg of dexamethasone twice daily during treatment with WB-XRT is important. The methotrexate dose in the EMA-CO regimen is increased to 1 g/m^2 and 30 mg of folinic acid every 12 hours for 3 days starting 32 hours after the infusion begins. Surgical excision or stereotactic XRT in selected patients can be given simultaneously with systemic chemotherapy. Cure rates with brain metastasis approach 50% to 80%.

RESISTANT DISEASE

- Diagnosis of resistance to first line therapy in low risk GTN is by: a persistent elevation over 3 consecutive samples, or an increase over 2 consecutive samples lasting > 2 weeks. For patients with a hCG < 100 IU/L, they can be considered for change to single agent dactinomycin after failing methotrexate or they can be treated with EMA-CO. For patients who fail single agent treatment with a hCG level > 100–300 IU/L, they should be treated with combination EMA-CO chemotherapy.
- In stage I resistant disease a switch to the other single-agent chemotherapy drug is indicated. A hysterectomy or local uterine resection may be considered in addition to chemotherapy if there is persistent disease.
- Stage II resistant disease is treated in a similar fashion as that for stage I resistant disease. Hysterectomy with ovarian preservation may be offered if this is the sole site of resistant disease.
- Stage III resistant disease:
  - For stage III low-risk resistant disease, treatment with MAC or EMA-CO should follow single-agent chemotherapy.
  - For high-risk stage III resistant disease, treatment with other regimens is indicated. These include MAC, CHAMOCA, VPB, VIP, or ICE.
- Stage IV resistant disease: second-line combination chemotherapy with MAC, CHAMOCA, VPB, VIP, or ICE is indicated. Hysterectomy with ovarian preservation may be indicated if this appears to be the sole site of resistant disease.

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RECURRENT DISEASE

- At diagnosis, reimaging with a CT of the chest, abdomen, and pelvis and MRI of the brain should be obtained. If all are negative, it may be helpful to then perform a lumbar puncture.
- Experimental imaging techniques can be employed to include anti-hCG radioisotope scanning and PET.
- If there are lung metastases and this appears to be the only site of resistant disease on comprehensive workup, a thoracotomy with lobectomy may be considered. If there are isolated liver metastases, a wedge resection may also be considered.

FOLLOW-UP

- For stages I to III, weekly quantitative beta hCG levels are drawn until they normalize for 3 weeks. Monthly quantitative beta hCG then continue until they are normal for 6–12 consecutive months.
- For stage IV disease it is important to follow beta hCG levels monthly for 2 years after the weekly beta hCG levels have normalized.
- Contraception with oral contraceptive pills (OCPs) (preferably) or another form of reliable contraception is important. Pregnancy may be attempted after 6 to 12 months of normal beta hCGs. IUD's are not recommended due to the risk of uterine perforation.

NOTABLE TRIALS

- GOG 55: 266 patients were randomly assigned to either OCP versus barrier method contraception after molar evacuation. The median time to spontaneous regression in the OCP group was 9 weeks, compared to the median time to regression in the barrier group of 10 weeks. Twice as many patients in the barrier group became pregnant in the immediate follow-up period; 23% of patients receiving OCPs had postmolar trophoblastic disease versus 33% of patients using barrier methods. OCPs are the preferred method of contraception after evacuation of a hydatidiform mole (5).
- GOG 79: patients with nonmetastatic GTD were initially treated with 30 mg/m^2 of weekly IM MTX. If no major toxicity was encountered, the weekly dose was escalated by 5 mg/m^2 at 3-week intervals until a maximum dose of 50 mg/m^2 each week was achieved. 81% had a complete response to weekly IM MTX. Duration of therapy ranged from 3 to 19 weeks, with a median of 7 weeks. No major dose limiting toxicity occurred, thus 50 mg/m^2 is acceptable dosing (6).
- GOG 79 follow-up study: this study evaluated 62 patients with nonmetastatic GTD who were initially treated with 40 mg/m^2 weekly of IM MTX. If no major toxicity was encountered, the weekly dose was escalated by 5 mg/m^2 at 2-week intervals until a maximum dose of 50 mg/m^2 per week was achieved; 74% had a complete response. Duration of therapy ranged from 3 weeks to 16 weeks with a median of 7 weeks. No major toxicity occurred. The 40 mg/m^2 dose of weekly IM MTX therapy is no more effective and of similar toxicity to the 30 mg/m^2 regimen (7).
- GOG 174: this trial evaluated 216 eligible patients with a WHO score of 0 to 6 and metastatic disease limited to lung lesions less than 2 cm, adnexa, or vagina, and/or histologically proven nonmetastatic choriocarcinoma. Patients were

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randomized to either biweekly IV actinomycin D 1.25 mg/m^2 versus weekly IM methotrexate 30 mg/m^2. Biweekly actinomycin D was superior to weekly methotrexate (CR 70% vs. 53%; $p = 0.03$). If the risk score was 5 to 6, or the diagnosis was choriocarcinoma, the CR to methotrexate was 9% and the CR was 42% with actinomycin D. Primary chemotherapy should then consist of actinomycin D in these intermediate and high-risk patients (8).

- GOG 242: this was a phase II study evaluating efficacy and safety of second uterine curettage in low risk nonmetastatic gestational trophoblastic neoplasia (GTN). 64 patients were enrolled and 24 (40%) were cured after second curettage without need for any chemotherapy. One uterine perforation occurred. Surgical failure occurred in 59% of women and was found more commonly in the age extremes. Four uterine hemorrhages occurred, and one new lung metastasis was observed. At the second curettage, histopathologic discrepancy changed the diagnosis (PSTT and placental nodule) for four patients. Higher WHO score trended to lower rate of second curettage cure (9).
- GOG 275: a phase III randomized trial of pulse actinomycin-D versus multiday methotrexate for the management of low risk GTN. This is an international phase III randomized trial of pulse actinomycin D versus multiday methotrexate for treatment of low-risk GTN. Results pending.

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