23 - 94 Gynecologic Malignancies

94 Gynecologic Malignancies

Patients in first relapse may be treated with either conventionaldose salvage chemotherapy or high-dose salvage chemotherapy with autologous stem cell rescue. There is controversy concerning which approach is optimal. Some institutions advocate for risk stratification, with more favorable prognosis patients receiving conventional-dose chemotherapy and worse prognosis patients receiving high-dose che motherapy. The most commonly utilized conventional-dose regimen includes paclitaxel, ifosfamide, and cisplatin (TIP). High-dose chemo therapy consists of initial salvage therapy followed by stem cell harvest and then two or three cycles of high-dose carboplatin and etoposide (CE) with stem cell rescue. A large retrospective analysis has com pared conventional-dose salvage chemotherapy to high-dose salvage chemotherapy in patients in first relapse. This study reports a more favorable outcome with high-dose salvage chemotherapy across nearly all risk groups. However, given the retrospective nature of this study and the controversy concerning optimal approaches, an international randomized trial comparing conventional-dose chemotherapy (TIP) to high-dose chemotherapy with autologous stem cell rescue (TI-CE) has completed accrual and results are forthcoming. Some patients who experience disease progression after conven tional-dose salvage chemotherapy may successfully be treated with high-dose salvage chemotherapy with autologous stem cell rescue. Patients with disease progression after high-dose salvage chemo therapy may be treated with subsequent chemotherapy regimens that include gemcitabine/oxaliplatin, gemcitabine/paclitaxel, epirubicin/ cisplatin, and oral etoposide. While these patients may benefit from third-line chemotherapy, few will achieve durable disease control. Select patients with relapsed but resectable disease may be candidates for salvage or so-called “desperation” surgery. Studies of molecularly targeted agents and immune checkpoint inhibitors in this population have to date been generally disappointing. Patients who experience disease progression >2 years after chemo therapy are considered to have “late relapse.” Late relapse appears to have a different biology than early relapse. These patients tend to have more chemotherapy-resistant disease. Patients with late relapse usu ally have nonseminomatous GCT with elevation of serum AFP. Many of these patients experience recurrence in the retroperitoneum many years after first-line chemotherapy, and this likely represents residual retroperitoneal disease that was not controlled after first-line therapy. These patients are best approached with salvage surgery. ■ ■EXTRAGONADAL GERM CELL TUMORS Approximately 5% of patients who present with GCTs have extrago nadal primaries. These mainly originate in the mediastinum or retro peritoneum. Patients suspected of extragonadal GCT should undergo scrotal ultrasound to exclude a gonadal primary. Extragonadal semi nomas have a similar excellent prognosis as their gonadal

counterparts and are approached the same. Mediastinal nonseminomatous GCTs are classified as poor risk and are treated with either four cycles of BEP or four cycles of VIP. These patients frequently require postchemotherapy thoracic surgery for residual disease. For this reason, some advocate avoiding bleomycin in this patient population. Klinefelter's syndrome is associated with an increased risk of mediastinal nonseminomatous GCTs. Rarely, mediastinal nonseminomatous GCTs are associated with hematologic disorders including acute myeloid leukemia. Nonsemi nomatous GCTs arising in the retroperitoneum do not have a worse prognosis than their gonadal counterparts. Many patients who present with extragonadal GCTs will undergo core needle biopsy for diagno sis. However, select patients with extragonadal tumors and definitive elevation of serum tumor markers may initiate chemotherapy without a tissue diagnosis. Cancers of unknown primary are defined as histologically proven metastatic malignancy in which the primary site is not obvious. A subgroup of patients with cancer of unknown primary have occult GCTs. Male gender, age <65 years, midline tumors, and nonsmok ing status increase the likelihood of this presentation. Pathology may demonstrate a poorly differentiated malignant neoplasm. Immunohis tochemical staining is used to exclude lymphoma. Tumor may be ana lyzed by fluorescence in situ hybridization for i(12p), which confirms

the diagnosis. Even if the diagnosis is not certain, patients should be treated with cisplatin-based chemotherapy, which will cure up to 20% of this patient group.

■ ■TESTICULAR NON–GERM CELL TUMORS Rarely, patients may develop testicular non-GCTs. These include nonHodgkin's lymphoma, most commonly occurring in men over the age of 50; sex cord stromal tumors including Leydig cell tumors and Sertoli cell tumors; mesothelioma of the tunica vaginalis; and paratesticular sarcoma. Metastasis to the testis is rare, most commonly occurring in patients with advanced prostate cancer and melanoma. ■ ■SURVIVORSHIP AND LATE EFFECTS Because most patients with testicular GCT will experience long-term survival, survivorship care is important. Since primary care physicians will follow many of these patients, an understanding of the physical, psychological, and social late effects is important. Late effects are defined as health problems that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be related to the underlying cancer or to the treatment the patient received. In longterm survivors of testicular GCT, increased cardiovascular risk and increased secondary malignancies have been reported. Patients treated with cisplatin-based chemotherapy have an increased risk of hyperten sion, hyperlipidemia, metabolic syndrome, and cardiovascular events. Patients treated with high cumulative doses of etoposide (e.g., patients who receive standard chemotherapy, relapse, and then receive salvage high-dose chemotherapy) may experience up to a 1–2% risk of devel oping acute myeloid leukemia, typically 2–3 years after completing therapy and associated with an 11q23 translocation. Patients treated with radiation therapy, cisplatin-based chemotherapy, or both have an increased risk of developing secondary solid malignancies. CHAPTER 94 Gynecologic Malignancies ■ ■FURTHER READING King J et al: Testicular cancer: Biology to bedside. Cancer Res 81:5369, 2021. Lobo J et al: Molecular biomarkers with potential clinical application in testicular cancer. Mod Pathol 36:100307, 2023. Pluta J et al: Identification of 22 novel susceptibility loci associated with testicular germ cell tumors. Nat Commun 12:4487, 2021. Travis LB et al: Adolescent and young adult germ cell tumors: Epi demiology, genomics, treatment, and survivorship. J Clin Oncol 42:696-706, 2024. David Spriggs

Gynecologic

Malignancies OVARIAN CANCER ■ ■INCIDENCE AND PATHOLOGY Ovarian cancer remains a leading cause of cancer deaths in American women, ranking behind lung, breast, colon, and pancreatic cancers. The ovary is responsible for hormone production and egg produc tion, including maturation and ovulation with the supporting cyclical production of sex steroid hormones. These complex biologic func tions are linked to populations of stromal cells, ovarian germ cells, and the enveloping epithelial cells. Malignancies arising from each group include multiple histologic variants, each with unique neoplastic behaviors. Epithelial tumors are, by far, the most common histologic variant of ovarian neoplasms; they may be benign (50%), frankly malignant (33%), or of borderline malignancy (low malignant poten tial) (16%). In adnexal masses detected by imaging or physical exam,

age influences risk of malignancy; tumors in younger women are more likely benign. In the malignant group, the most common tumors are epithelial. In the group of the ovarian epithelial malignancies are the serous tumors (60–70%), mucinous tumors (10%), endometrioid tumors (10–15%), and clear cell tumors (10–15%) tumors. The dis tribution of histologic types varies in different parts of the world. The less common stromal tumors arise from the ancillary, supportive cells such as steroid hormone–producing cells and likewise have different phenotypes and clinical presentations. Most stromal tumors do not produce estrogen, but ectopic hormone production can be seen in certain subtypes. Tumors arising in the ovarian germ cell lineage are generally similar in biology and behavior to testicular tumors in males, although their intraperitoneal location alters some metastatic behaviors

(Chap. 93). Ovarian tissue may also host metastatic epithelial tumors arising from breast, colon, gastric, and pancreatic primaries. Bilateral ovarian masses from metastatic mucin-secreting gastrointestinal can cers are termed Krukenberg tumors. Consideration of other potential malignancies is part of the diagnostic workup of ovarian masses.

■ ■OVARIAN CANCER OF EPITHELIAL ORIGIN Epidemiology An American woman has approximately a 1 in 72 lifetime risk (1.6%) of developing ovarian cancer, with the majority of affected women developing epithelial tumors. In 2024 in the United States, ~19,710 cases of ovarian cancer are expected to be diagnosed, with >13,270 deaths. Sporadic (not familial) epithelial tumors of the ovary have a peak incidence in women in their fifties and sixties, although age at presentation ranges from the third decade to the eight ies and nineties. Ovarian cancer risk has been linked to an interactive mixture of epidemiologic, environmental, and genetic factors. Nul liparity, obesity, diet, infertility treatments, talc exposure, and possibly hormone replacement therapy have all been linked to an increase in risk. Protective factors include the use of oral contraceptives, multipar ity, tubal ligation, aspirin use, and breast-feeding. Other epidemiologic factors such as the historical use of perineal talc agents remain contro versial. The mechanisms underlying the various protective factors are largely unknown, but it is increasingly clear that dysplasia and in situ cancers are seen within the fallopian tube and probably are the original site for a large percentage of cancers. PART 4 Oncology and Hematology Genetics and Pathogenesis Ovarian cancers are divided into type 1 cancers and the more aggressive type 2 variant. The type 1 can cers are characterized by low-grade histology and generally indolent behavior. These tumors include the low malignant potential tumors, low-grade endometrial and mucinous histologies, and clear cell can cers (which are more aggressive). Genetic alterations in type 1 cancers include mutations in KRAS, BRAF, PTEN, and PIK3CA. In contrast, type 2, high-grade serous epithelial ovarian cancers show serial genetic

changes in the fallopian tube with loss of BRCA1/2 function and TP53 mutation leading to intraepithelial cancer in the luminal epithelium. Following these early genetic events, additional mutations in these transformed cells lead to tumor cell shedding, metastasis, and invasion. These type 2, poorly differentiated, serous cancer cells can then spread to the ovaries and the peritoneal cavity, aided by the ovarian cancer cell's expression of MUC16 and binding to mesothelin-expressing cells. Genetically, type 2 serous ovarian cancer is classically a disease characterized by loss of TP53 (95%) and BRCA1/2 function in nearly all cases. Widespread amplifications and deletions rather than single-gene point mutations or common gene fusions are also present. Low preva lence but statistically recurrent somatic mutations in seven other genes including NF1, RB1, and CDK12 were also seen. The most common heritable abnormality linked to ovarian cancer is a germline mutation in either BRCA1 (chromosome 17q12–21) or BRCA2 (chromosome 13q12–13). These genes are essential parts of the homologous DNA repair machinery for double-stranded DNA break repair. Individuals inheriting a single copy of a mutant allele have an increased lifetime risk of breast (46–87% for BRCA1; 38–84% for BRCA2) and ovarian cancer (39–63% for BRCA1; 16.5–27% for BRCA2). Many of these women have a family history that includes multiple cases of breast and/ or ovarian cancer at an early age. Male breast cancer, pancreatic cancer,

and prostate cancer are also linked to familial BRCA2 mutations. The most common malignancy in women carrying germline BRCA1/2 mutations is breast carcinoma, although women harboring germline BRCA1 mutations also have a marked increased risk of developing ovarian malignancies in their forties and fifties. Women harboring a mutation in BRCA2 have a lower penetrance of ovarian cancer with onset typically in their fifties or sixties. Other uncommon germline mutations of other genes encoding proteins linked to homologous DNA repair (e.g., PALB2) can also contribute to cancer risk, although the frequency of mutation and magnitude of risk increment are much lower. Germline BRCA1/2 testing is recommended for all incident epi thelial ovarian cancers to detect probands to identify relatives for early therapeutic intervention. Women with these high-risk germline muta tions are advised to undergo prophylactic removal of fallopian tubes and ovaries after completing childbearing, ideally before age 40. Early prophylactic salpingo-oophorectomy is highly protective. Salpingooophorectomy also appears to protect these women from subsequent breast cancer (risk reduction 50%). Prophylactic salpingectomy is almost certainly the key part of any surgical prophylaxis strategy for ovarian cancer prevention. Although less common, women with type II Lynch syndrome caused by mutations in one of the DNA mismatch repair genes (MSH2, MLH1, MLH6, PMS1, PMS2) are at risk for ovarian and endometrial cancer. Like BRCA1/2-related cancers, these cancers develop earlier than sporadic ovarian cancer. Neoplasms of the ovary tend to be painless unless they undergo torsion. Nonspecific gastrointestinal symptoms like bloating and early satiety are common at presentation, probably related to compression of local organs or due to symptoms from metastatic disease. Women with ovarian tumors also may have an increased incidence of symptoms including pelvic discomfort, bloating, and perhaps changes in urinary or bowel pattern. Unfortunately, these same symptoms are common in primary care and are frequently dismissed by either the woman or her health care team until later stages of disease. The pathogenic factors and timing of spread beyond the ovary are still not well understood. The most common symptoms at presentation of advanced disease include a period of progressive complaints of nausea, early satiety, bloating, indigestion, constipation, and abdominal pain. Signs include the rapid increase in abdominal girth due to the accumulation of ascites that typically alerts the patient and her physician that the concurrent gas trointestinal symptoms are likely associated with malignant pathology. Radiologic evaluation typically demonstrates a complex adnexal mass with

ascites, carcinomatosis, and pelvic, para-aortic, and mesenteric adenopathy in advanced disease. Positron emission tomography (PET) scans are generally not required. Laboratory evaluation often demon strates a markedly elevated serum CA-125, the shed mucin component (MUC16) associated with, but not specific for, ovarian cancer. Ovarian cancers are divided into four stages, with stage I tumors confined to the ovary, stage II malignancies confined to the pelvis, and stage III con fined to the peritoneal cavity and retroperitoneal nodes (Table 94-1). These three stages are subdivided, with the most common presenta tion, stage IIIC, defined as tumors with bulky intraperitoneal disease or positive lymph node involvement. About 70% of women present with stage III disease. Stage IV disease includes women with parenchymal metastases (liver, lung, spleen) or, alternatively, abdominal wall or pleu ral disease. The 30% of patients not presenting with stage III disease are roughly evenly distributed among the other stages. Screening Advanced ovarian cancer is a highly lethal condition. It is curable in early stages but seldom curable in advanced stages; hence, screening continues to be of considerable interest. Early-stage tumors often secrete excessive amounts of normal proteins that can be measured in the serum such as CA-125, mesothelin, and HE-4. Never theless, the incidence of ovarian cancer in the middle-aged female pop ulation is very low, with only ~1 in 2000 women between the ages of 50 and 60 carrying an asymptomatic and undetected tumor. Large, welldesigned screening studies, even in the mutated BRCA1/2 families, have thus far failed to decrease ovarian cancer mortality in prospective testing. Circulating DNA approaches have also been unsuccessful so far. Screening for ovarian cancer is currently not recommended outside

TABLE 94-1 Staging and Survival in Gynecologic Malignancies STAGE OVARIAN 5-YEAR SURVIVAL, % ENDOMETRIAL 5-YEAR SURVIVAL, % CERVIX 5-YEAR SURVIVAL, %

— — Carcinoma in situ

I Confined to ovary 88–95 Confined to corpus

> “ 90 Confined to uterus

II Confined to pelvic organs 70–80 Involves corpus and cervix III Intra-abdominal spread to omentum, diaphragm, or lymph nodes 20–40 Extends outside the uterus but not outside the true pelvis IV Spread outside abdominal cavity, parenchymal spread, and pleural effusion cytology 10–20 Extends outside the true pelvis or involves the bladder or rectum of a clinical trial, but a careful history for familial cancers and directed genetic testing for susceptibility genes are definitely appropriate. TREATMENT Ovarian Cancer Epithelial ovarian cancer can be divided into distinct “disease states” for the purpose of treatment selection, as shown in Fig. 94-1. Detection by ultrasonography generally can identify a complex ovarian mass as “suspicious,” but surgery by a skilled gynecologic oncologist remains the preferred initial diagnostic and therapeutic option for an isolated adnexal mass or a more involved picture of peritoneal involvement. The amount of residual visible cancer at the end of a primary operation is strongly predictive of outcome and is paired with histology, grade, and stage to determine prognosis and treatment. Metastatic disease to the ovary can be seen from primary tumors of the colon, appendix, stomach (Krukenberg tumors), and breast. Needle biopsy of adnexal masses is contraindicated to avoid malignant

contamination of the peritoneal cavity with malignant cells. Typically, women undergo laparoscopic evaluation Primary Treatment First Remission Maintenance Consolidation Diagnostic surgery Primary debulking Interval debulking HRD abnormal -> Poly-(ADP-ribose)- polymerase inhibitor for 2 y Platinum complex

- taxane Chemotherapy HRD wild type No treatment Platinum-Resistant/Recurrent Disease Persistent cancer following platinum treatment or recurrence within 6 months of last platinum dose Single-agent treatment with or without bevacizumab: Liposomal doxorubicin, topotecan, docetaxel, weekly paclitaxel, gemcitabine, vinorelbine, pemetrexed, etoposide, bevacizumab, mirvetuximab, soravtansine Investigational therapy Death From Disease FIGURE 94-1 Disease states model of epithelial ovarian cancer and its treatment. Each box represents a relatively homogenous group of patients who share a palette of potential treatment choices and have a similar prognosis. The arrows indicate that a single patient may move from one state to another during the course of her illness, and the choice of treatments will become different in her new disease state. HRD, homologous recombination deficiency.

~75 Invades beyond uterus but not to pelvic wall

45–60 Extends to pelvic wall and/ or lower third of vagina, or hydronephrosis

~20 Invades mucosa of bladder or rectum or extends beyond the true pelvis

and unilateral salpingo-oophorectomy for diagnostic purposes. If pathology reveals a primary ovarian malignancy or the laparoscopy proves disseminated disease is present, then the procedure should be followed by a total hysterectomy, removal of the remaining tube and ovary, omentectomy, and pelvic node sampling along with biopsies of the peritoneal cavity and diaphragms. This extensive surgical procedure is performed because ~30% of tumors that, by visual inspection, appear to be confined to the ovary have already disseminated to the peritoneal cavity and/or surrounding lymph nodes. As with axillary dissections in breast cancer, node sampling is diagnostic, but full lymphadenectomy appears to provide little or no additional therapeutic advantage over nodal sampling. The tar get outcome of an ovarian cancer surgery is always an R0 resection (no visible residual cancer). The less favorable “optimal resection” (no residual disease >1 cm in size) is still clinically useful, and the prognosis of those patients is much better than that of patients who are left with >1 cm of disease at the end of surgery. These “suboptimally debulked” patients derive very little benefit from their surgery. If large deposits of unresectable residual tumor are anticipated, the surgery should be delayed until after several cycles of neoadjuvant chemotherapy. Such “interval debulking” surgery CHAPTER 94 Gynecologic Malignancies Cure of Disease Platinum-Sensitive Relapse Subsequent Remission • Interval surgery • Maintenance therapy with poly-(ADP-ribose)- polymerase inhibitors • Carboplatin with either liposomal doxorubicin, paclitaxel, or gemcitabine • Bevacizumab

achieves similar results to primary surgery with diminished surgical morbidity and more timely chemotherapy. Patients without gross residual disease (R0 resection) after resection have a median sur vival in excess of 60 months, compared to 28–42 months for those left with macroscopic tumor or those undergoing interval debulk ing, regardless of treatment strategy.

After appropriate surgical treatment, primary chemotherapy will consist of combination treatment with paclitaxel and carbo platin. Primary chemotherapy can be delivered intravenously, or alternatively, some therapy can be directly administered into the peritoneal cavity via an indwelling catheter. The intraperitoneal approach is technically more difficult and is increasingly replaced by carboplatin and paclitaxel, which appears to offer similar results. Although interest in immunotherapy or chemoimmunotherapy has been high, immunotherapeutics have not yet improved primary chemotherapy. With optimal debulking surgery and platinum-based chemo therapy, 70% of women who present with advanced-stage tumors show tumor reduction, and 40–50% experience a complete remis sion with normalization of their CA-125, computed tomography (CT) scans, and physical examination. For women with evidence of functional homologous DNA repair defects, administration of oral poly-ADP ribose polymerase inhibitors (PARPi) such as nirapa rib, olaparib, or rucaparib will improve survival outcomes when administered at the completion of intravenous chemotherapy as consolidation. These drugs substantially delay recurrence and pro vide survival advantages as well. In the majority of patients, disease still recurs within 1–4 years from the completion of their primary therapy. CA-125 levels often increase as a first sign of relapse, and CT scan findings are eventually confirmatory. Recurrent disease is often successfully managed for years but rarely cured, despite a growing panel of chemotherapeutic agents and antibody-drug con jugates. Additional surgical therapy does not appear to extend sur vival in randomized trials. Patients with a treatment-free interval are often best treated with additional platinum doublets, combining carboplatin with liposomal doxorubicin, gemcitabine, or a taxane. Eventually all women who experience relapse develop chemother apy-refractory disease. Refractory ascites, poor bowel motility, and obstruction or tumor-infiltrated aperistaltic bowel are all common premorbid events. Limited surgery to relieve intestinal obstruction, localized radiation therapy to relieve pressure or pain from masses, or palliative chemotherapy may be helpful. Agents with >15% response rates include gemcitabine, topotecan, liposomal doxorubi cin, and bevacizumab. Five-year survival correlates with the stage of disease: stage I, 90–95%; stage II, 70–80%; stage III, 25–40%; stage IV, 10–15% (Table 94-1). Prognosis is improved by lower histologic grade and presence of BRCA1 or BRCA2 germline mutation. PART 4 Oncology and Hematology ■ ■UNCOMMON OVARIAN TUMORS Low Malignant Potential Tumors (Borderline Tumors)

These type 1 tumors are found in younger women (age 30–50 years) and are indolent in behavior, and few of these patients will succumb to their tumors (10-year survival may approach 98%), although recur rence is not uncommon. Certain features, such as micropapillary histology and microinvasion, are linked to more aggressive behavior. Tumors of low malignant potential have different mutations includ ing mutations BRAF or KRAS and cyclin-dependent kinase inhibitor (CDKN) 2A/2B deletion. Borderline tumor patients are managed pri marily by surgery, but targeted therapy for the RAS/RAF pathway and hormonal treatments sometimes have benefit. Stromal Tumors Approximately 7% of ovarian neoplasms are stromal tumors, with ~1800 cases expected each year in the United States. Ovarian stromal tumors or sex cord tumors are most common in women in their fifties or sixties, but tumors can present at any age. These tumors arise from the mesenchymal components of the ovary, including both steroid-producing cells and fibroblasts. Most of these

tumors are indolent tumors with limited metastatic potential and pres ent as unilateral solid masses. These tumors primarily are discovered by the detection of an abdominal mass, sometimes

with abdominal pain due to ovarian torsion, intratumoral hemorrhage, or rupture. Rarely, stromal tumors can produce estrogen and present with breast tender ness as well as precocious puberty in children, menstrual disturbances in reproductively active women, or postmenopausal bleeding. In some women, estrogen-associated secondary malignancies, such as endo metrial or breast cancer, may present as synchronous malignancies. Sertoli-Leydig tumors often present with hirsutism and virilization due to increased production of androgens. Hormonally inert tumors include fibromas, which present as solitary masses often in association with ascites and occasionally hydrothorax, also known as Meigs's syn drome. A subset of these tumors presents in individuals with a variety of inherited disorders that predispose them to mesenchymal neoplasia including Ollier's disease (juvenile granulosa cell tumors) and PeutzJeghers syndrome (ovarian sex cord tumors). The treatment of these tumors is primarily complete surgical resection, without adjuvant che motherapy. Chemotherapy with carboplatin and paclitaxel is generally reserved for either unresectable or multiply recurrent tumors. Germ Cell Tumors of the Ovary Germ cell tumors, like their counterparts in the testis, are cancers of germ cells. These totipotent cells contain the programming for differentiation to essentially all tis sue types, and hence, the germ cell tumors include a histologic menag erie of bizarre tumors, including benign teratomas (dermoid cysts) and a variety of malignant tumors, such as dysgerminoma, immature teratomas, yolk sac malignancies, and choriocarcinomas. Benign tera toma (or dermoid cyst) is the most common germ cell neoplasm of the ovary and often presents in young women. These tumors include a complex mixture of differentiated tissue including tissues from all three germ layers. In older women, these differentiated tumors can develop malignant transformation, most commonly squamous cell carcinomas. Malignant germ cell tumors include dysgerminomas, yolk sac tumors, immature teratomas, and embryonal and choriocarcinomas. Germ cell tumors can present at all ages, but the peak age of presentation tends to be in adolescents. Typically, these tumors will become large ovarian masses, which eventually present as palpable low abdominal or pelvic masses. Like sex cord tumors, torsion or hemorrhage may present urgently or emergently as acute abdominal pain. Some germ cell tumors produce elevated levels of human chorionic gonadotropin (hCG) or α-fetoprotein (AFP). Unlike epithelial ovarian cancer, these tumors have a higher proclivity for nodal or hematogenous metastases. Germ cell tumors typically present in women who are of childbearing age, and because bilateral tumors are uncommon (except in dysgermi noma, 10–15%), the typical treatment is unilateral oophorectomy or salpingo-oophorectomy with lymph node sampling. Most commonly, women with advanced malignant germ cell tumors typically receive bleomycin, etoposide, and cisplatin (BEP) chemotherapy, in an analo gous fashion to the treatment of testicular cancers. In the majority of these women, even those with advanced-stage disease, cure is expected. Dysgerminoma is the ovarian counterpart of testicular seminoma and is highly curable. Although the tumor is highly radiation-sensitive, radiation produces infertility in many patients. BEP chemotherapy is as effective or more so without causing infertility. FALLOPIAN TUBE CANCER Transport of the egg to the uterus occurs through the fallopian tube, with the distal ends of these tubes composed of fimbriae that drape about the ovarian surface and capture the egg as it erupts from the ovarian cortex. As described above, the majority of type 2 ovarian cancers are now thought to arise from the tubal epithelium. Fallopian tube malignancies are typically of serous histology and share the same biology and recommended treatment approaches as serous ovar ian cancer. These tumors often present as clinically isolated adnexal masses, but like ovarian cancer, these tumors spread relatively early throughout the peritoneal cavity. Fallopian tubal cancers have a natural history and treatment that are essentially identical to ovarian cancer (Table 94-1).

CERVICAL CANCER ■ ■ETIOLOGY AND GENETICS Cervical cancer is the second most common and the most lethal malignancy in women worldwide. Infection with high-risk strains of human papillomavirus (HPV) is the primary neoplastic-initiating event in the vast majority of women with invasive cervical cancer. This double-stranded DNA virus infects epithelium near the transformation zone of the cervix where underlying columnar epithelium becomes squamous epithelium. More than 60 types of HPV are known, with ~20 types having the ability to generate high-grade dysplasia and malignancy. HPV16 and 18 are the types most frequently associated with high-grade dysplasia, but types 31, 33, 35, 52, and 58 are also considered to be high-risk variants. The large majority of sexually active adults are exposed to HPV, and most women clear the infection without specific intervention. The 8-kb HPV genome encodes seven early genes, most notably E6 and E7, which can bind to RB and p53, respectively. High-risk types of HPV encode E6 and E7 molecules that are particularly effective at inhibiting the normal cell cycle checkpoint functions of these regulatory proteins, leading to immortalization but not full transformation of cervical epithelium. A minority of women will fail to clear the infection, with subsequent HPV integration into the host genome. Over as little as a few months to several years, some of these persistently infected women develop worsening dysplasia, a premalignant condition that, untreated, can progress to cervical carci noma. Complete transformation to cancer occurs over a period of years and almost certainly requires the acquisition of other genetic mutations within the infected and immortalized epithelium. In 2024, more than half a million new cases of cervical cancer will occur worldwide, with an estimated >300,000 deaths. Cancer incidence is particularly high in women residing in Central and South America, the Caribbean, and southern and eastern Africa. The mortality rate is disproportionately high in Africa. In the United States, an estimated 13,960 women will be diagnosed with cervical cancer in 2024 and ~4300 women will die of the disease. In the integrated genomic characterization of cervical cancer by The Cancer Genome Atlas (TCGA), integration of HPV sequences was found in all of the HPV18-linked cancers and over three-quarters of the HPV16 cancers. The cervical tumors also showed a charac teristic APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; a family of cytidine deaminases that edit DNA and are endogenous mutagenic enzymes) pattern of mutagenesis, with ERBB3, CASP8, and TGFRB2 identified as significantly mutated genes presumably linked to progression from dysplasia to carcinoma. In the much smaller number of HPV-negative cancers, which are more com mon in older women, mutations in oncogenes KRAS, ARID1A, and PTEN were frequently seen. The clinical behavior of these cancers is likely to be different. ■ ■HPV INFECTION AND PREVENTION The Pap smear is the primary detection method for asymptomatic preinvasive cervical dysplasia of squamous epithelial lining during a gynecologic exam. Because the progression from dysplasia to cervi cal cancer takes several years, annual (or longer interval) screening and prevention strategies that detect precancerous dysplasia and carcinoma in situ can be implemented successfully. Annual or bian nual cervical scraping for cytology (Pap smear) is highly effective in reducing the incidence of cervical cancer by early detection and subsequent surgical treatment of premalignant disease. The incorpo ration of HPV testing by polymerase chain reaction (PCR) or other molecular techniques increases the sensitivity of detecting cervical pathology but at the cost of lower sensitivity in that it identifies many women with transient infections who require no specific medical intervention. Unfortunately, both the collection of a Pap smear and its cytologic evaluation require infrastructure beyond the means of many middle- and low-income countries. High-throughput, low-technology prevention strategies and point-of-care testing are needed to identify and treat women bearing high-risk cervical dysplasia to prevent cancer development.

A primary prevention strategy relies on HPV vaccines. In the United States, the Gardasil-9 vaccine protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Vaccination of girls and women between ages 9 and 45 years is recommended with three injections (0, 2, and 6 months). Vaccination before the initiation of sexual activity dra matically reduces the rate of high-risk HPV infection and subsequent dysplasia. Vaccination of both boys and girls is increasingly considered to reduce the risk of HPV-induced cancers of the pharynx. Vaccinated women are still at risk for HPV infection and still benefit from standard Pap smear screening.

■ ■CLINICAL PRESENTATIONS Risk Factors Clinical risk factors include the prevalence of highrisk HPV subtypes in the population and HPV infection–linked features such as a high number of sexual partners, early age of first intercourse, and history of venereal disease. Smoking is a cofactor; heavy smokers have a higher risk of dysplasia with HPV infection. HIV infection, especially when associated with low CD4+ T-cell counts, is associated with a higher rate of high-grade dysplasia and likely a shorter latency period between infection and invasive disease. Histo logically, the majority (80%) of cervical malignancies are squamous cell carcinomas associated with HPV, but adenocarcinomas are also HPV related, and both arise in the transitional zone of the endocervi cal canal; the lesions in the canal or cervical glands may not be seen by visual inspection of the cervix and can be missed by Pap smear screening. Other malignancies, such as vulvar cancer, anal cancer, and, increasingly, pharyngeal cancer, are also linked to HPV infection. CHAPTER 94 Gynecologic Malignancies Diagnosis of Cervical Cancer Early cancer of the cervix is asymptomatic, and this biology underlies the recommendations for routine gynecologic care. Larger, invasive carcinomas often have symptoms or signs including postcoital spotting or intermenstrual cycle bleeding or menometrorrhagia. Foul-smelling or persistent

yellow discharge may also be present. Symptoms such as pelvic or sacral pain suggest lateral extension into the pelvic nerve plexus by either the primary tumor or a pelvic node metastasis and indicate advanced-stage disease. Likewise, flank pain from hydronephrosis from ureteral compression or deep-venous thrombosis from iliac vessel compression suggests either extensive nodal disease or direct extension of the primary tumor to the pelvic sidewall. The most common finding upon physical exam is a visible tumor on the cervix, but deeper tumors in the cervical os and glands should be considered. Larger tumors may be identified by inspection and biopsied directly. Staging of cervical cancer is performed by expert clinical exam. Stage I cervical tumors are confined to the cervix, whereas stage II tumors extend into the upper vagina or paracervical soft tissue (Fig. 94-2). Stage III tumors extend to the lower vagina or the pelvic sidewalls, whereas stage IV tumors invade the bladder or rectum or have spread to distant sites. While radiographic studies are not part of the formal clinical staging of cervical cancer, treatment planning requires them for appropriate therapy. CT can detect hydronephrosis indicative of pelvic sidewall disease but is not accurate at evaluating other pelvic structures. Mag netic resonance imaging (MRI) is more accurate at estimating uterine extension and paracervical extension of disease into soft tissues typi cally bordered by broad and cardinal ligaments that support the uterus in the central pelvis. Very small stage I cervical tumors can be treated with a variety of surgical procedures, but minimally invasive surgery has inferior outcome compared to standard open hysterectomy. In young women desiring to maintain fertility, radical trachelectomy removes the cervix with subsequent anastomosis of the upper vagina to the uterine corpus; however, subsequent pregnancies may be more problematic. Patients with large stage I cervical tumors (4 cm) confined to the cervix and all stage II to IV patients are treated with radiation therapy in combination with

cisplatin-based immunochemotherapy with concurrent PD-1 blockers. This multimodality treatment can offer the patient with advanced-stage disease a 40–80% chance of cure depending on the clinical circumstances. Immunotherapy with PD-1 blockade, cisplatin, paclitaxel, bevacizumab, and tisotumab vedotin are generally considered as appropriate palliative choices for metastatic

Staging of cervix cancer Stage

I II III IV Disease to pelvic wall or lower 1/3 vagina Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina Confined to cervix Extent of tumor Carcinoma in situ 65% 85% 5-year survival 100% 4% Stage at presentation 28% 47% Uterine cavity Fundus Fallopian tube Uterine wall Corpus IIB Internal os IIIB Cervix IIA IIIA External os Vagina FIGURE 94-2 Anatomic display of the stages of cervix cancer defined by location, extent of tumor, frequency of presentation, and 5-year survival. PART 4 Oncology and Hematology cervical cancer patients. Secondary chemotherapy confers minimal improvement in most patients. Additional immunotherapies targeting HPV antigens are potential avenues for improved outcomes in recur rent, unresectable cancers of the cervix. UTERINE CANCER ■ ■EPIDEMIOLOGY Several different tumor types arise in the uterine corpus. Most tumors arise in the glandular lining and are endometrial adenocarcinomas. Benign (leiomyomas) and malignant smooth muscle tumors (leiomyo sarcomas) can also arise in the uterus and have very different clinical features. The endometrioid histologic subtype is the most common gynecologic malignancy in the United States. In 2024, the American Cancer Society predicted that 66,200 new cancers of the uterine corpus are expected in 2024 with 13,030 resulting deaths. Development of these tumors is a multistep process, with estrogen playing an impor tant early role in driving endometrial gland proliferation. Relative overexposure to this class of hormones is the principal risk factor for the subsequent development of endometrioid tumors. In contrast, pro gestins drive glandular maturation and are protective. Hence, women with high endogenous or pharmacologic exposure to estrogens, espe cially if unopposed by progesterone, are at higher risk for endometrial cancer. Obese women, women treated with postmenopausal estrogens, or women with estrogen-producing tumors are at higher risk for endo metrial cancer. In addition, long-term treatment with tamoxifen, which has antiestrogenic effects in breast tissue but can show weak estrogenic effects in uterine epithelium, is associated with an increased risk of endometrial cancer. Genetics Women with a germline mutation in one of a series of DNA mismatch repair genes associated with the Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC) syndrome, are at increased risk for endometrioid endometrial carcinoma. These individuals have germline mutations in MSH2, MLH1, and, in rare cases, PMS1 and PMS2. Individuals who carry these mutations typi cally have a family history of cancer and are at markedly increased risk for colon cancer and modestly increased risk for ovarian cancer and a variety of other tumors. Middle-aged women with HNPCC carry a 4% annual risk of endometrial cancer and a relative overall risk of ~200fold as compared to age-matched women without HNPCC. In sporadic cancers, secondary events such as mutation of the PI3K gene or the loss of the PTEN tumor-suppressor gene likely serve as secondary genetic “hits” in the carcinogenesis related to estrogenic excess. The molecular

events that underlie less common endo metrial cancers such as clear cell and papillary serous tumors of the uterine corpus are not well understood. Invades bladder, rectum or metastasis ■ ■PATHOLOGY Approximately 75–80% of endometrial cancers are adenocarcinomas and have been characterized as type 1 (estrogenlinked) endometrial cancers and type 2 cancers that have less

clear associations with estrogens (clear cell cancers, serous cancers, and mucinous cancers). Endo metrial serous cancers show TP53 loss of function and behave clinically more like ovarian cancers with high risk for sys temic recurrence. Prognosis for endome trial cancer depends on stage, histologic grade, and depth of myometrial invasion. 7% 35% 21% Pelvic side wall ■ ■CLINICAL PRESENTATION The majority of women with tumors of the uterine corpus present with post menopausal vaginal bleeding due to shedding of the malignant endometrial lining. Premenopausal women often will present with atypical bleeding between typical menstrual cycles. These signs typically bring a woman to the attention of health care providers, and the majority of women have early-stage disease in which the tumor is confined to the uterine corpus and, consequently, have a high cure rate. Diagnosis is typically established by endometrial biopsy. Type 1 tumors may spread to pelvic or para-aortic lymph nodes and are gen erally subjected to sentinel lymph node biopsy at the time of primary surgery. Serous tumors tend to have patterns of spread similar to highgrade serous ovarian cancer, and patients may present with omental/ peritoneal disease and sometimes ascites. Some women presenting with uterine sarcomas will present with pelvic pain. Uterine sarcomas (carcinosarcomas and leiomyosarcomas) commonly are found by detection of symptomatic large pelvic masses that may not be associ ated with dysfunctional vaginal bleeding. TREATMENT Uterine Cancer Most women with endometrial cancer have disease that is local ized to the uterus (75% are stage I, Table 94-1), and definitive treatment typically involves a hysterectomy with removal of the ovaries and fallopian tubes. The resection of lymph nodes does not improve outcome, but sentinel node resection provides important staging and prognostic information. Node involvement defines stage IIIC disease, which is treated with immunochemotherapy. Tumor grade and depth of invasion are two key prognostic vari ables in early-stage tumors, and women with low-grade and/or minimally invasive tumors (<50% myometrial penetration) are typically observed after definitive surgical therapy. Patients with high-grade tumors or tumors that are deeply invasive (stage IB) are at higher risk for pelvic recurrence or recurrence at the vaginal cuff, which is typically prevented by intravaginal brachytherapy. It is now routine to test all endometrial cancers for microsatellite instability (MSI) with a larger number of mutations in the tumor. MSI cancers, when recurrent or present at an advanced stage, are likely to respond to immune checkpoint therapy and PD-1–targeted therapy should be part of treatment for those patients. Women with regional metastases or metastatic disease (3% of patients) with low-grade tumors can be treated with progesterone or tamoxifen. In contrast, poorly differentiated tumors lack hormone receptors and are typically unresponsive to hormonal manipulation. The role of adjuvant chemotherapy in stage I–II disease is generally restricted to serous endometrial cancers. For more advanced-stage

cancers (stage III–IV), chemotherapy and/or immune checkpoint blockade are administered because of the higher rates of recurrent systemic disease. Carboplatin and paclitaxel combinations with immune targeting agents are the current standard of care. Chemo therapy for metastatic disease is delivered with palliative intent. Even patients with advanced cancer and known mismatch repair deficits may respond well to immunotherapy with antagonists of the PD-1/PD-L1 axis. Lenvatinib and pembrolizumab (even for microsatellite-stable tumors) have become the most common second-line treatments. Other potentially active treatments include bevacizumab and mammalian target of rapamycin (mTOR) inhibi tors (e.g., temsirolimus). Newer antibody-drug conjugates may have good responses in patients with expression of the target antigens. Carcinosarcomas of the uterus (also called Müllerian tumors) con tain both mesenchymal and epithelial components but will often respond to paclitaxel and platinum complex therapy. Other uterine sarcomas require an entirely different approach and need histologyspecific consideration.

The most common are the leiomyosarcomas of the uterus, which are treated with docetaxel/gemcitabine at recurrence but do not appear to benefit from adjuvant therapy. Ifosfamide/doxorubicin and trabectedin can have some benefit in refractory disease. GESTATIONAL TROPHOBLASTIC TUMORS Gestational trophoblastic diseases represent a spectrum of neoplasia from benign hydatidiform mole to choriocarcinoma due to persistent trophoblastic disease associated most commonly with molar preg nancy but occasionally seen after normal gestation. The most common presentations of trophoblastic tumors are partial and complete molar pregnancies. These represent approximately 1 in 1500 conceptions in developed Western countries. The incidence widely varies globally, with areas in Southeast Asia having a much higher incidence of molar pregnancy. Regions with high molar pregnancy rates are often associ ated with diets low in carotene and animal fats. ■ ■RISK FACTORS Trophoblastic tumors result from the outgrowth or persistence of placental tissue. They arise most commonly in the uterus but can also arise in other sites such as the fallopian tubes due to ectopic pregnancy. Risk factors include poorly defined dietary and environmental factors as well as conceptions at the extremes of reproductive age, with the incidence particularly high in females conceiving at younger than age 16 or older than age 50. In older women, the incidence of molar preg nancy might be as high as one in three, likely due to increased risk of abnormal fertilization of the aged ova. Most trophoblastic neoplasms are associated with complete moles, diploid tumors with all genetic material from the paternal donor (known as uniparental disomy). This is thought to occur when a single sperm fertilizes an enucleate egg that subsequently duplicates the paternal DNA. Trophoblastic proliferation occurs with exuberant villous stroma. If pseudopregnancy extends out past the 12th week, fluid progressively accumulates within the stroma, leading to “hydropic changes.” Fetal development does not occur in complete moles. Partial moles arise from the fertilization of an egg with two sperm cells; hence, two-thirds of genetic material is paternal in these triploid tumors. Hydropic changes are less dramatic, and fetal development can often occur through late first trimester or early second trimester, at which point spontaneous abortion is common. Laboratory findings will include excessively high hCG and high AFP. The risk of persistent gestational trophoblastic disease after partial mole is ~5%. Complete and partial moles can be noninvasive or invasive. Myometrial invasion occurs in no more than one in six complete moles and a lower portion of partial moles. ■ ■PRESENTATION OF INVASIVE TROPHOBLASTIC DISEASE The clinical presentation of molar pregnancy is changing in developed countries due to the early detection of pregnancy with home pregnancy

kits and the very early use of Doppler and ultrasound to evaluate the early fetus and uterine cavity for evidence of a viable fetus. Thus, in these countries, the majority of women presenting with trophoblastic disease have their moles detected early and have typical symptoms of early pregnancy including nausea, amenorrhea, and breast tenderness. With uterine evacuation of early complete and partial moles, most women experience spontaneous remission of their disease as moni tored by serial serum β-hCG levels. These women require no chemo therapy. Patients with persistent elevation of β-hCG or rising β-hCG after uterine evacuation have persistent or actively growing gestational trophoblastic disease and require therapy. Most series suggest that between 15 and 25% of women will have evidence of persistent gesta tional trophoblastic disease after molar evacuation.

In women who lack access to prenatal care, presenting symptoms can be life-threatening, including the development of preeclampsia or even eclampsia. Hyperthyroidism can also be seen with very

high β-hCG values. Evacuation of large moles can be associated with lifethreatening complications including uterine perforation, volume loss, high-output cardiac failure, and adult respiratory distress syndrome (ARDS). For women with evidence of rising β-hCG or radiologic confir mation of metastatic or persistent regional disease, prognosis can be estimated through a variety of scoring algorithms that identify women at low, intermediate, and high risk for requiring multiagent chemother apy. In general, women with widely metastatic nonpulmonary disease, very elevated β-hCG, and prior normal antecedent term pregnancy are considered at high risk and typically require multiagent chemotherapy at an expert center for cure. Even very advanced gestational tropho blastic disease is almost uniformly curable when managed by an expert in this rare malignancy. CHAPTER 94 Gynecologic Malignancies TREATMENT Invasive Trophoblastic Disease Management of invasive trophoblastic disease should be 100% curative, and complex patients should only be managed by clini cians experienced in this disease. The management for a persistent and rising β-hCG after evacuation of a molar conception is typi cally chemotherapy, although surgery can play an important role for chemotherapy-resistant disease that is isolated in the uterus (especially if childbearing is complete) or to control hemorrhage. For women wishing to maintain fertility or with metastatic disease, the preferred treatment is chemotherapy or immunotherapy tar geting the PD-1 axis. Trophoblastic disease is exquisitely sensitive to chemotherapy, and guided by serial serum β-hCG testing, suc cessful, curative treatment is the rule. Single-agent treatment with dactinomycin or methotrexate cures 90% of women with low-risk disease. Patients with high-risk disease (very high β-hCG levels, presentation ≥4 months after pregnancy, brain or liver metastases, failure of methotrexate therapy) are typically treated with mul tiagent chemotherapy (etoposide, methotrexate, and dactinomycin, alternating with cyclophosphamide and vincristine [EMA-CO]), which is typically curative even in women with extensive metastatic disease. A regimen of cisplatin and etoposide alternating with etoposide/methotrexate/dactinomycin is used for the highest-risk patients. In the highest-risk patients with liver, lung, and brain metastases, hemorrhage from the rich tumor vasculature is a major risk during chemotherapy initiation. Cured women may become pregnant again without evidence of increased fetal or maternal complications. ■ ■FURTHER READING Longo DL: Personalized medicine for primary treatment of serous ovarian cancer. N Engl J Med 381:2471, 2019. Lu KH, Broaddus RR: Endometrial cancer. N Engl J Med 383:2053, 2020. Moore KN et al: Mirvetuximab soravtansine in FRα-positive,

platinum-resistant ovarian cancer. N Engl J Med 389:2162, 2023.

Revision #1
Created 2026-01-06 16:31:53 UTC by Omar Ayman
Updated 2026-01-06 16:31:53 UTC by Omar Ayman