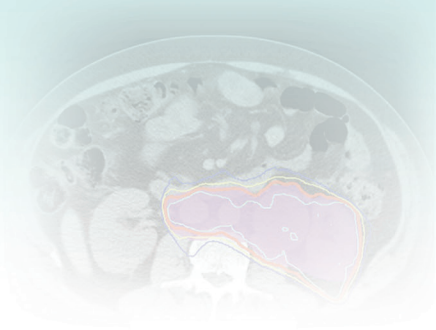
CHAPTER

61 Ovarian Cancer



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INCIDENCE AND ETIOLOGY

Ovarian cancer constitutes 3% of all cancer diagnosed in women and 5% of all cancer-related deaths. In 2015 the estimated incidence of ovarian cancer in the United States was 21,290 cases with an estimated 14,180 deaths. The lifetime risk in the general population is 1.4%. The molecular events involved in the carcinogenesis of ovarian cancer are still unclear; however, environmental, hormonal, and genetic risk factors have been identified through epidemiologic studies.

PREVENTION AND EARLY DETECTION

The focus of ovarian cancer screening is to attempt to identify women with early-stage disease. The most common techniques used in screening are serum CA-125 and ultrasonography. Multiple trials have shown a low positive predictive value (PPV) of screening the general population and an expected higher PPV when screening high-risk populations. Until further evidence of the utility of screening is available it is not recommended for the general population.

Most hereditary ovarian cancer is associated with a germline mutation in the *BRCA1* or *BRCA2* gene. For patients with an identified *BRCA1* and *BRCA2* mutation, screening has been recommended, despite its unproven value. Prophylactic salpingo-oophorectomy at the completion of childbearing is recommended.

BIOLOGIC CHARACTERISTICS

Epithelial ovarian cancer comprises approximately 90% of all ovarian cancers, 75% of which are of serous histology. In the first two decades of life, ovarian germ cell tumors (GCTs) constitute almost 70% of all ovarian tumors, a third of which are malignant. Sex cord and stromal tumors are rare, although they account for 90% of all hormone-producing tumors.

STAGING EVALUATION

Ovarian cancer is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) staging system based on the patterns of spread. In early-stage disease, comprehensive surgical staging is pertinent because the extent of disease determines indications for subsequent treatment. Advanced stage disease (III/IV) exists in 70% of patients at diagnosis.

PRIMARY THERAPY

The primary treatment for ovarian cancer is surgical. In early-stage disease a comprehensive surgical staging procedure is completed. In patients with epithelial stage IA or GCTs, fertility-sparing surgery may be performed. For patients with advanced stage, cytoreductive surgery is performed with the purpose of removing all macroscopic disease if feasible.

ADJUVANT THERAPY

Patients with early-stage, low-grade epithelial ovarian cancer do not benefit from adjuvant therapy. The current recommendation for all other patients is adjuvant combination chemotherapy (chemo) with carboplatinum and paclitaxel. Certain histologies such as clear cell may benefit from adjuvant radiation therapy (RT).

Patients with GCTs (other than stage I dysgerminoma and stage IA grades 1 and 2 immature teratoma) are commonly treated with bleomycin, etoposide, and a platinum-based regimen or with etoposide and a platinum-based regimen.

The benefit of adjuvant chemo for sex-cord and stromal tumors has not been proven.

ADVANCED DISEASE

Advanced ovarian cancer is treated with cytoreductive surgery and postoperative combination chemo. The most commonly used regimen is six cycles of carboplatin and paclitaxel. Intraperitoneal chemo (cisplatin with or without paclitaxel) and intravenous (IV) paclitaxel improves survival and should be considered in optimally debulked patients (<1 cm gross residual tumor), although the regimen for optimal therapeutic ratio is not defined. Maintenance chemo has not been shown to be beneficial and cannot be recommended. Maintenance bevacizumab has demonstrated a modest increase in progression-free survival (PFS) and no difference in overall survival (OS) or quality of life.

The majority of patients with ovarian cancer enter a state of remission on completion of surgery and postoperative chemo, but about 85% experience relapse and die of disease.

RADIATION THERAPY

Abdominopelvic RT is an effective adjuvant treatment for some well-defined patient groups with ovarian cancer, although platinum-based chemo has become the preferred modality. The role of RT in advanced stage disease as consolidation therapy sequential to surgery and chemo is controversial. Certain patients with early-stage disease and specific histologies may benefit from adjuvant RT. RT for palliation is effective and should be recommended in patients with localized symptoms.

PALLIATION

Because disease relapse is usually incurable, the principal aim is to prolong symptom-free survival and palliate symptoms. The benefit of second-line chemo is dependent on the disease-free interval from completion of treatment to relapse. Patients who experience relapse early, less than 6 months from completion of treatment, are "platinum resistant," and their response rates are low, whereas those who experience relapse with a longer treatment-free interval are "platinum sensitive" and have a higher response rate.

Secondary debulking, which is surgery performed to remove tumor relapse, is considered in patients with late relapse and resectable tumor. RT for palliation is an effective modality in patients with symptoms related to localized disease. Patients should be considered for clinical trials or symptomatic measures when a low probability of response to therapy is expected.

Ovarian cancer is the fifth-most common cause of cancer death among women, and the leading cause of gynecologic cancer-related death in the United States.[1] The incidence of ovarian cancer for 2015 in the United States was projected to be 21,290 cases, thus constituting 3% of all cancer diagnosed in women. The lifetime risk in the general population is 1.4%. In 2014 the expected number of deaths attributed to ovarian cancer was projected to be 14,180, accounting for 5% of all cancer-related deaths.[2]

Ovarian cancer is one of the most clinically challenging cancers to treat. Cure rates are low as symptoms are nonspecific and diagnosis is usually late in the disease course. It primarily spreads throughout the peritoneal cavity, and maximal cytoreduction, of proven benefit, often requires complex surgical procedures. The majority of patients experience relapse and will succumb to their disease, making ovarian cancer a psychologically and physically challenging disease for patients and their caregivers.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Ovarian cancer is infrequent before the age of 40, with a median age at diagnosis of 63 years. The age-specific incidence increases with age, reaching its peak in the eighth decade, with an incidence of 57 per 100,000 in the 70- to 74-year age group[3] (Figure 61-1). Incidence rates and the number of cancer-related deaths have been relatively stable over the past three decades.

Five-year OS is the typically reported end point for epithelial ovarian cancer and is approximately 45%. The survival is significantly better for the 30% of patients with localized disease, with 5-year OS of 93%. However, approximately 70% of women are diagnosed when disease has spread, with expected 5-year OS of 20% to 30%.[1,4-6] Women diagnosed younger than age 65 have higher 5-year OS (65.8%) in comparison to those older than age 65 (32.9%).

Etiology

The molecular events involved in the carcinogenesis of ovarian cancer are still unclear. However, environmental, hormonal, and genetic risk factors have been identified through epidemiologic studies.

Environmental Risk Factors

Country of residence and race has been associated with an increased risk of ovarian cancer. Women living in North America and in northern Europe have the highest risk. The incidence is highest among white women, is intermediate among black women, whereas Hispanic, Asian, and American Indian women have the lowest reported risk.[7] Many dietary factors have been evaluated in regard to the risk of ovarian cancer, including a diet high in meat and calories, antioxidant intake (e.g., vitamins A, C, and E), and lactose or coffee consumption, although none has consistently been shown to significantly alter the risk.[7-10]

Hormonal Factors

Hormonal factors including increased parity, age at first birth before age 25 years, history of breast-feeding, oral contraceptive use, and tubal ligation have been shown in multiple epidemiologic studies to decrease the risk of developing ovarian cancer by 25% to 60%.[11-13] Hormone-replacement therapy has been shown in the Million Women Study and in a more recent Danish cohort study to be a risk factor for ovarian cancer.[14,15] Both studies demonstrated a 1.5- to 2-fold increased risk of developing ovarian cancer in current users of hormone-replacement therapy. The protective effects of parity, multiple births, oral contraceptive use, and breast-feeding support the "incessant ovulation" theory, in which each ovulatory cycle causes damage to the ovarian epithelium and then the process of aberrant repair becomes an initial step in carcinogenesis.[16] Therefore, the more ovulatory cycles a woman has in her lifetime, the higher her risk of developing ovarian cancer. A second hypothesis attributes an increased risk to excessive

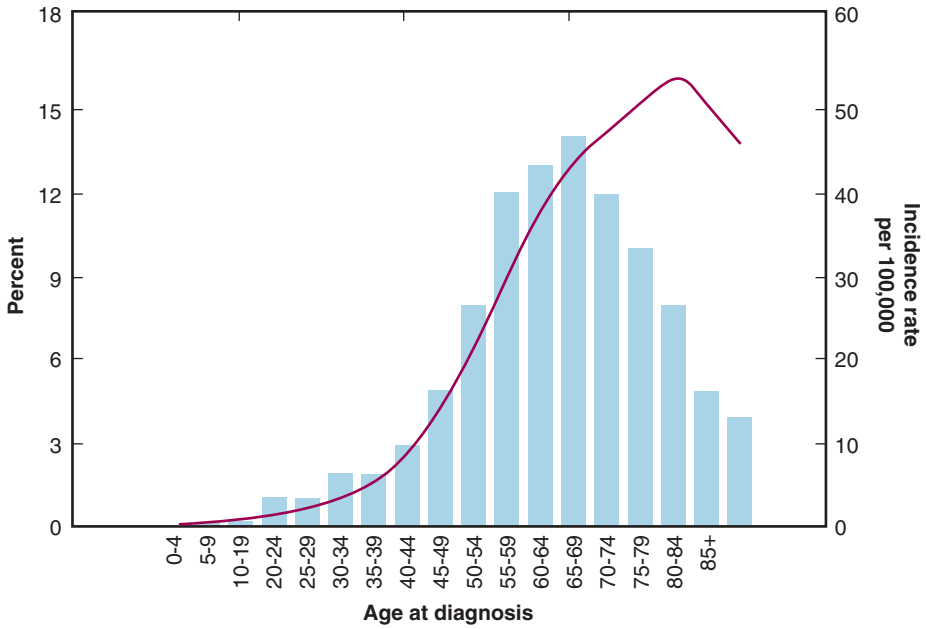


Figure 61-1 Incidence rates by age for ovarian cancer.
Data from Yancik R, Ries LG, Yates JW: Ovarian cancer in the elderly. An analysis of Surveillance, Epidemiology, and End Results Program data. Am J Obstet Gynecol 154:639–647, 1986.

gonadotropin secretion.[17] Because of the high concentration of gonadotropins, estrogenic stimulation occurs, leading to the entrapment of epithelial cells in inclusion cysts, which further leads to cell proliferation and malignant transformation.[17,18] Oral contraceptive use and pregnancy, in addition to stopping ovulation, lower gonadotropin levels; therefore, both traditional risk reducers are in concordance with both theories. Hence, patients treated for infertility with ovarian stimulation would be expected to have an increased risk of ovarian cancer. Although an increased risk of predominantly borderline tumors was reported in a cohort of women treated for infertility with prolonged use of the ovulation stimulator, clomiphene citrate, the data have not been consistent. Both a large Danish population-based cohort study and a retrospective cohort study of almost 10,000 U.S. women treated with a spectrum of infertility medications did not support the correlation between infertility medication and ovarian cancer.[19,20]

Genetic Factors

Only 15% of all ovarian cancers are attributable to known genetic mutations, that is, 13% to the hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2* germline mutations) and 2% to the hereditary nonpolyposis colon cancer syndrome (*MLH1, MSH2,* and *MSH6* mutations).[19,21,22] Women with hereditary nonpolyposis colon cancer (HNPCC) syndrome have an increased risk of developing multiple types of cancer, including colon, endometrial, and ovarian cancer. The lifetime risk of women with HNPCC of developing ovarian cancer is 15% to 25%.[23] The frequency of *BRCA* mutations differs among ethnic groups. Founder (recurrent) mutations have been identified in specific ethnic groups; for example, up to 40% of all women who are of Ashkenazi Jewish descent with ovarian cancer carry one of three founder mutations.[24] Additional founder mutations have been found among women who are Polish and French-Canadian.[25,26] Women who harbor a *BRCA1* mutation have a lifetime risk of 30% to 40% for developing ovarian cancer. Women with a *BRCA2* mutation have a 15% to 25% lifetime risk of developing ovarian cancer, depending on the location of the mutation in the genes; a higher risk is correlated with a mutation in the ovarian cancer cluster region.[27] Women with a *BRCA1* or *BRCA2* mutation also have an increased risk of fallopian tube cancer. The lifetime risk of breast cancer for carriers of *BRCA1* and *BRCA2* mutations is 50% to 85%.

PREVENTION AND EARLY DETECTION

Screening and Prophylactic Surgery

The majority of women with ovarian cancer presents with advanced disease and therefore has a poor long-term prognosis. In contrast, those patients who are diagnosed when the cancer is limited to the ovaries have a good prognosis, with a 5-year OS of 80% to 90%.[28] Unlike cervical cancer, it is unclear that there is an orderly progression from limited to extensive disease. Nevertheless, the focus of ovarian cancer screening is to identify women with early-stage disease. The most common screening techniques used to date are ultrasonography and serum CA 125. The latter is an antigenic serum tumor marker detected by radioimmunoassay that is elevated in 80% of epithelial ovarian cancers.

Two large randomized trials have addressed the question of the yield of screening for ovarian cancer: the U.S. National Institutes of Health (NIH) Prostate Lung Colorectal and Ovary Study (PLCO) and the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[29,30] UKCTOCS randomly assigned 202,638 women who were postmenopausal to a control group (no screening) versus two different arms of screening (annual transvaginal ultrasonography or annual CA 125 screening and further transvaginal ultrasonography if results were elevated). To date only the prevalence data of UKCTOCS has been reported showing that the majority of cases diagnosed were at advanced stage. PLCO randomly assigned 39,115 women to screening (annual CA 125 and transvaginal ultrasonography) versus usual care (i.e., no screening). In 2011, the results of PLCO were published; 118 deaths caused by ovarian cancer were found in the intervention group and 100 deaths in the usual care group (relative risk [RR], 1.18; 95% confidence interval [CI], 0.82 to 1.71).[31] They found that 15% of women with false-positive results who underwent surgery experienced at least one serious complication and therefore concluded that this screening in the general population did not reduce ovarian cancer mortality and was associated with surgical complications. Although there are minor differences in trial design between the two aforementioned studies (including a stricter screening protocol, higher quality control, and the use of a trend in CA125 and not an absolute number in the UKCTOCS trial), at this point in time there is no proven survival benefit for screening the general population and it is not recommended.

Multiple trials have shown the expected higher PPV when screening high-risk populations.[32-37] For patients with an identified *BRCA* mutation, screening has been recommended at the NIH Consensus Conference on Ovarian Cancer despite the absence of proven survival benefit.[38]

New directions examining potential novel serum markers using proteomics and genomics are being explored.[39-41] The majority of studies are evaluating the sensitivity and specificity of combinations of markers. Visintin et al,[40] from Yale University, studied concentrations of a combination of six proteins, including leptin, prolactin, osteopontin, insulin-like growth factor 2, macrophage inhibitory factor, and CA 125 in 156 patients with newly diagnosed ovarian cancer and 362 healthy controls. They reported a sensitivity of 95.3% and a specificity of 99.4% for the detection of ovarian cancer. These promising results require additional validation studies.

The value of genetic counseling for patients with an identified *BRCA* mutation or HNPCC has been established because the management decision making is complex. Individualized recommendations are made based on the specific risk, patient age, and her reproductive goals. Prophylactic salpingo-oophorectomy in women with a *BRCA* mutation reduces the risk of gynecologic cancer (ovarian and fallopian tube) by 85% to 96%.[42-45] There remains an approximately 1% risk of primary peritoneal cancer.[42-44] In addition, the risk of developing subsequent breast cancer was reduced by 50% to 60%.[46] The NIH consensus panel in 1995 recommended prophylactic oophorectomy for women at high-risk at age 35 or after the completion of childbearing.[38] Because of the emerging evidence supporting the hypothesis that ovarian cancer originates in the fimbriated end of the fallopian tube, there is growing acceptance to perform bilateral salpingectomies at time of hysterectomy if oophorectomy is not indicated to potentially lower the risk of ovarian cancer. However, more data is needed before guideline recommendations can be made.

BIOLOGIC CHARACTERISTICS AND PROGNOSTIC FACTORS

Currently prognostic clinicopathologic and biologic variables are used to predict survival probability. It is hoped that molecular markers will soon be identified that better define risk.

Clinicopathologic Factors

The surgically determined stage of disease is directly correlated with survival. The Surveillance, Epidemiology and End Results (SEER) database, for patients diagnosed between 2006 and 2009, reported a 5-year OS of 44.2% for all stages; 91.9% for stage I, 72.0% for stage II, and 27.3% for combined stages III and IV.[47]

Histologic grade, based in the FIGO system on architectural features, that is, the ratio of glandular or papillary structures versus solid tumor growth within a tumor, is an important prognostic factor in epithelial ovarian cancer.[48-50] Patients with high-grade (poorly differentiated) tumors have worse outcomes than those with low-grade (well-differentiated) tumors. In patients with early-stage (IA to IB) low-grade tumors, a 94% 5-year OS has been reported with surgery alone.[51]

The effect of histologic cell type has generally been of less important prognostic significance than other factors although the stage distribution at presentation and response to chemotherapy differ markedly. However, it has been suggested that early-stage endometrioid and mucinous cell types have a better prognosis than serous and clear cell adenocarcinoma, but when grade and cell type are evaluated, histologic cell type has not been found to be an independent factor.[52,53]

In patients with advanced-stage disease, chemotherapy sensitivity is an important prognostic factor. Therefore, patients with serous histology have a better prognosis than those with the more chemoresistant tumors (e.g., mucinous and clear cell).[54]

Patient age at diagnosis and performance status are independent prognostic factors.[55,56] However, tumor size and bilaterality are not prognostic.

The volume of residual tumor at the completion of a cytoreductive surgery for advanced ovarian cancer is directly correlated with survival.[55] Chi et al[57] from Memorial Sloan Kettering Cancer Center have shown that an aggressive primary cytoreduction, including extensive upper abdominal procedures, resulted in increased optimal cytoreduction rates and significantly improved progression-free survival (PFS) and OS in patients with advanced ovarian carcinomas. However, it remains controversial whether it is primarily the aggressiveness of the surgery, the biology of the tumor, or both that contribute to prognosis.

Elevated preoperative and postoperative CA 125 levels, a reflection of volume of disease, and the time frame over which the level declines during chemotherapy have been shown to correlate with prognosis.[58]

Biologic Factors

The cellular DNA content, as determined by flow-cytometric analysis, is an independent prognostic factor. Aneuploid (versus diploid) DNA content in ovarian tumors is correlated with more aggressive biologic behavior and a worse clinical course.[59,60]

Molecular markers, including both abnormalities in oncogene products (e.g., ERBB2 [HER2/neu], ERBB3 [HER3]), and suppressor gene products (e.g., TP53) correlate with prognosis.[61,62] Many additional biologic markers, including markers of proliferation and of DNA repair, together with newer studies on loss of human leukocyte antigen class I, KLK6, and KLK13, have been reported,[63,64] although their significance has not yet been established.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathogenesis

Ovarian cancers are classified by their histology. The largest categories are epithelial (approximately 80% of all ovarian cancers), germ cell, and sex cord and stromal. The traditional view of the pathogenesis of epithelial ovarian cancer asserts that all tumor subtypes share a common origin in the surface epithelium of the ovary, which is repeatedly disrupted by ovulation and consequent release of inflammatory cytokines, capable of damaging DNA.[65,66] This increases the susceptibility to malignant transformation. Moreover, numerous invaginations into the stroma develop as the ovary ages and these invaginations further form cortical inclusion cysts.[67] Epithelial cells in the cysts are exposed to high hormone levels that induce proliferation and are susceptible to malignant transformation if there has been previous DNA damage.

This putative mechanism of carcinogenesis has not been supported by identification of a precursor lesion in the ovary. Prophylactic surgery in patients with a genetic predisposition to breast and ovarian cancer has led to pathological evaluation of removed ovaries and fallopian tubes for the presence of early cancers or noninvasive lesions. Isolated foci of cancer have been seen in the fallopian tube but rarely have small isolated cancers been found confined to the ovary.[68-70] These observations led many authors to conclude that the fallopian tube may be the primary site of cancers, which if diagnosed later in the course of disease would have been classified as a primary ovarian cancer.[70-72]

Pathways of Spread

Epithelial ovarian cancer spreads through four mechanisms: (1) direct contiguous spread to adjacent organs, (2) transcoelomic in the peritoneal cavity, (3) lymphatic, and (4) hematogenous (rare).

Transcoelomic: The most common pattern of spread is through exfoliation of cancer cells into the peritoneal cavity. The cells move with the peritoneal fluid circulation from the pelvis into the right paracolic gutter to the upper abdomen and return to the pelvis through the left abdomen. The cells attach to the surface of intraabdominal organs and grow into masses. They uncommonly invade intraabdominal organs (e.g., the bowel, liver, or spleen).

Lymphatic: Lymphatic spread of cancer cells to the pelvic and paraaortic lymph nodes is common. Spread above the diaphragm to the supraclavicular nodes occurs through retroperitoneal dissemination.

Hematogenous: Hematogenous spread of ovarian cancer to the parenchyma of vital organs (e.g., liver or lungs) is rare at diagnosis, occurring in less than 5% of all cases. Systemic metastases can be seen at time of relapse, when disease is widespread throughout the pelvis and abdomen.

Direct spread: Ovarian cancer cells can spread through direct extension from the ovary to adjacent organs; the most common site being the fallopian tube.

Histologic Classification

Epithelial ovarian carcinomas are subclassified based on histologic cell type: serous, mucinous, endometrioid, clear cell, and transitional. They are also divided into borderline (also called tumors of low malignant potential) and invasive. Borderline tumors of the ovary are defined as those with epithelial atypia without stromal invasion. They generally are associated with an excellent prognosis, with a nearly 100% 5-year OS when diagnosed at stage I.[73] Borderline tumors occur primarily in women of a younger age in comparison with invasive cancer.

Serous carcinoma is the most common histologic subtype of epithelial ovarian cancer.[74] It is characterized histologically by broad, branching papillae covered with stratified epithelial

cells. High-grade serous carcinoma contains large pleomorphic nuclei with many mitoses. Papillary fenestrations with slit-like fenestrations are common, there may be large areas of necrosis, and psammoma bodies may be present.

Low-grade serous ovarian carcinomas (micropapillary carcinomas) are tumors with grade-1 nuclear atypia, low-grade architecture, and low mitotic activity.[75] They are associated with extensive papillary architecture and often contain an abundance of psammoma bodies. Low-grade serous carcinomas may arise in association with borderline tumors and are distinct from high-grade serous tumors because they do not behave aggressively. The low-grade and borderline serous tumors frequently have mutations in BRAF and KRAS and lack TP53 mutations. Borderline serous ovarian tumors clinically behave in an intermediate manner between benign and malignant; that is, there may be peritoneal implants but most are noninvasive. The 5-year OS of stage III borderline serous tumors is approximately 85%, whereas that of stage III invasive serous cancer is only 20% to 30%.[6,76] Long-term follow-up of 276 patients with ovarian serous tumors of low malignant potential identified unresectable disease and invasive implants as significantly associated with decreased survival ($p < 0.001$).[77]

Mucinous cyst adenocarcinomas are diagnosed when the majority of the epithelial cells contain mucin and comprise approximately 15% of ovarian tumors. The majority are benign (80%), approximately 10% are borderline, and 10% are invasive. Microscopically, the malignant areas show back-to-back glands with malignant cells and little or no stroma. The epithelial cells are columnar or polygonal with eosinophilic or mucinous cytoplasm. Goblet cells and signet ring cells may be present, although if they are abundant a metastasis from a gastrointestinal origin should be considered. Invasive mucinous carcinoma of ovarian origin is rare and is usually diagnosed at an early stage.[78] Molecular studies have shown a link between borderline and invasive mucinous tumors.[79] Unlike serous ovarian cancers, individual tumors frequently show heterogeneity with benign, borderline, and invasive areas. On gross examination they are the largest of all ovarian tumors, are commonly unilateral, have a smooth surface, and are multilocular.

Endometrioid carcinomas comprise approximately 10% of all epithelial ovarian cancers and commonly arise in extrauterine endometrial tissue. Approximately one third of the cases are associated with endometriosis.[80] Adenocarcinomas associated with endometriosis may develop in association with proliferative adenofibromas and frequently occur after de novo malignant transformation of the endometrial epithelium. They are composed of epithelial cells and patterns similar to endometrial hyperplasia and neoplastic changes of the endometrium. Early-stage endometrioid carcinomas are bilateral in approximately 15% of cases. They are both cystic and solid and often are seen near foci of endometriosis. The grading is identical to that of primary carcinomas of the endometrium. Endometrioid tumors of the ovary carry genetic alterations in the phosphatase and tensin homolog (PTEN) similar to those in the endometrium.

Clear cell carcinomas of the ovary are adenocarcinomas in which most of their epithelial cells have clear cytoplasm, predominantly owing to glycogen, although part may be from mucin. They are easily recognizable under low power because of their unique architecture. They primarily have a papillary pattern with hyalinized stroma, although they can also have a more cystic, glandular, or solid pattern. Clear cell carcinomas are uncommon, comprising approximately 5% of all epithelial ovarian tumors in North America, and almost half are associated with endometriosis. Unlike serous cancers, patients predominantly present with stage I disease (50% to 60%), and when compared stage for stage to serous ovarian cancer, the prognosis seems to be worse.[81,82] However, in Japan, clear cell carcinoma of the ovary represents more than 20% of all epithelial ovarian cancer.[83] The prognosis of stage I clear cell carcinoma in Japan has been shown to be superior to that of serous ovarian cancer. Ovarian clear cell and endometrioid cancers have been shown clinically to be associated with endometriosis; however, the molecular events associated with this transformation have only recently been identified by Gilks et al with regard to ARID1A mutations.[84] They identified ARID1A mutations in 55 of 119 ovarian clear-cell carcinomas (46%), 10 of 33 endometrioid carcinomas (30%), and none of the 76 high-grade serous ovarian carcinomas. They further saw that ARID1A mutations and loss of BAF250a expression was found in tumors and atypical endometriosis but not in endometriotic lesions. These data implicate ARID1A as a tumor-suppressor gene disrupted in endometriosis associated carcinomas and can potentially be an early event in the transformation of endometriosis into cancer.

Transitional cell ovarian carcinomas have epithelial cells that resemble transitional cells of the urinary tract. They include both Brenner tumors (benign, borderline, or malignant) and transitional cell carcinomas. They may be pure or a component of a mixed epithelial tumor. Brenner tumors are mostly arranged in a trabecular pattern, with lipid-rich cells in the stroma. The epithelial cells have a pale, oval nucleus with a longitudinal groove ("coffee bean" nucleus). They are high-grade epithelial tumors that, by definition, do not include the elements of Brenner tumors. The tumor resembles transitional cell tumors originating in the bladder with broad papillae containing highly stratified, crowded cells. The cells have eosinophilic or clear cytoplasm, and the degree of nuclear atypia varies. Transitional cell carcinomas are bilateral in up to 20% of cases.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

More than 75% of epithelial ovarian cancers are diagnosed when disease has spread throughout the abdominal cavity. The most common presenting symptoms are abdominal discomfort, pain, or distension because of the presence of malignant masses or ascites throughout the peritoneal cavity. Gastrointestinal symptoms (e.g., nausea, early satiety, change in bowel habit/constipation, bloating) are also frequent at the time of diagnosis. Additional symptoms that may occur include fatigue, dysuria, and vaginal bleeding.

In patients with early-stage disease, symptoms are rare. Therefore, the diagnosis is predominantly made incidentally at the time of evaluation for nonrelated gynecologic complaints or by palpation of an asymptomatic ovarian mass. The majority of palpable ovarian masses in women who are premenopausal are benign. In contrast, any palpable mass in a woman who are postmenopausal has a high probability of being malignant.

Patient Evaluation and Diagnosis

Although the diagnosis of ovarian cancer is made at the time of surgery or by biopsy, benign diseases of the female genital tract such as functional cysts, endometriosis, and uterine myomas must be differentiated from ovarian cancer; therefore, patients who present with an adnexal mass must undergo a full evaluation, including history and physical examination. Pelvic ultrasonography and determination of CA 125 level are also used to assist in evaluating the malignant potential of the adnexal mass. A complex mass evident on ultrasound

evaluation containing irregular borders, solid elements with papillary projections, multiple irregular septa, and bilateral tumors is suggestive of malignancy. The use of additional abdominal and extra-abdominal imaging is dependent on the patient's specific complaints and the physical examination.

Serum CA 125 is elevated in 80% of women with epithelial ovarian cancer and is predominantly associated with serous ovarian cancer. It is seldom elevated in the mucinous subtype. In women who are postmenopausal aCA 125 higher than 65 U/mL was found to have a PPV of 98% and a negative predictive value (NPV) of 72%.[85]

Jacobs et al[86] proposed the "Risk of Malignancy Index" in 1990, estimating the risk of an adnexal mass being malignant in a specific patient. It has since been validated in many studies. The Risk of Malignancy Index incorporates the serum CA 125 level, ultrasound scan result (0, 1, or 3), and the menopausal state (0, premenopausal, 3, postmenopausal). These researchers defined a cutoff of 200 in which a sensitivity of 85% and a specificity of 97% for predicting malignancy were found.

Women who present with apparent advanced disease seen on ultrasonography or computed tomography (CT) need a full evaluation before deciding on optimal management. This includes a full personal and family history, physical examination, and assessment of surgical risk, which is pertinent to confirm the likely origin and probable extent of disease. Because most of the symptoms of advanced-stage ovarian cancer are nonspecific it is essential to confirm that the primary tumor is ovarian. Confusion with metastatic gastrointestinal tract malignancy can occur. Additional tests that may be required include serum CA 125 determination, imaging (e.g., chest radiography, CT, magnetic resonance imaging [MRI], barium enema), and upper or lower gastrointestinal endoscopies. Extensive disease may be judged initially unresectable and therefore indicate consideration of neoadjuvant chemotherapy rather than initial surgery.

Surgical Staging

Ovarian cancer is staged surgically according to the FIGO staging system, which was last revised in 1995. The patterns of spread and natural history of ovarian cancer form the basis of the system[28,87] (Table 61-1). The stage can be determined only after an exploration of the abdomen and pelvis, apart from the rare occasion in which stage IV disease may be documented by cytology positive pleural effusion, fine-needle aspiration of a supraclavicular node, or a liver metastasis. Comprehensive surgical staging is mandatory to determine subsequent treatment. When there is no macroscopic disease outside the ovary, an evaluation for microscopic disease must be performed. On entering the abdominal cavity, aspiration of ascites or peritoneal washings should be performed. The abdomen and pelvis should be thoroughly examined and palpated; any suspicious lesions should be sampled. The tumor should be removed intact if possible because spillage of malignant cells is suggested to worsen the prognosis.[88] The remaining ovary, uterus, and fallopian tubes should be removed unless fertility sparing is appropriate (premenopausal patient with a low-grade or borderline ovarian cancer). Pelvic and paraaortic lymph nodes should be systematically removed, an omentectomy performed, and random peritoneal biopsy specimens taken. Carnino et al showed that the detection of positive lymph nodes correlated with the number of lymph nodes removed (odds ratio [OR], 3.9 for more than 10 lymph nodes in comparison to 1 to 5; 95% CI, 1.0 to 15.4), therefore emphasizing the importance of systematic lymph node dissection.[89] Patients initially thought to have early-stage disease that undergo subsequent comprehensive surgical staging may be upstaged in up to 30% of the cases.[90]

TABLE 61-1 FIGO Staging for Carcinoma of the Ovary

Stage	Description
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites containing malignant cells. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites containing malignant cells. No tumor on the external surface; capsule intact
IC	Tumor either stage IA or IB but with tumor on the surface of one or both of the ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension or metastases to the uterus or fallopian tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB but with tumor on the surface of one or both of the ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none > 2 cm in diameter. Nodes negative
IIIC	Abdominal implants > 2 cm in diameter or positive retroperitoneal or inguinal lymph nodes or both
IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV

It has also been shown that it is important that a gynecologic oncologist perform the operation. The percent of properly staged women varies by type of surgical qualification and is 97%, 52%, and 35% when the staging was performed by a gynecologic oncologist, obstetrician/gynecologist, or general surgeon, respectively.[91]

PRIMARY TREATMENT OF OVARIAN EPITHELIAL CANCER

The selection of treatment for each individual patient presenting with epithelial ovarian cancer should be based on the extent of disease, performance status, and individual patient characteristics. Therapeutic options include surgery, chemotherapy, radiation, or a combination of modalities. The identification of biomarkers and subsequent exploration of novel targeting molecular therapies constitute an important direction of research and potential therapeutic opportunity.

Early-Stage Disease: Surgery and Chemotherapy

There is consensus that all patients should undergo comprehensive surgical staging as their primary treatment. Approximately one third of patients with epithelial ovarian cancer present with apparent localized disease confined to the ovaries or to the pelvis. When all patients undergo surgical staging, however, this number decreases to 10% to 15%. Because the percentage of patients with early-stage disease is small and their prognosis is good, it is difficult to conduct studies evaluating the yield of adjuvant treatment for this group of patients.

Two randomized trials—International Collaborative Ovarian Neoplasm Trial 1 (ICON1) and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial (ACTION)[92,93]—addressed the question of the efficacy of adjuvant chemo to improve survival in women with early-stage disease. Both trials randomized patients with early-stage disease to adjuvant platinum-based chemotherapy or no adjuvant treatment. The analysis of the combined trials showed an 8% difference in OS in favor of the adjuvant chemo arm (82% versus 74%, $p = 0.008$). Relapse-free survival (RFS) was also significantly better in the chemo arm of the trials (76% versus 65%, $p = 0.001$).

When the trials were analyzed separately, OS for all patients treated with chemo in comparison to those who did not receive adjuvant chemo in the ACTION trial was not found to be significantly better (hazard ratio [HR], 0.69; 95% CI, 0.44 to 1.08). On subgroup analyses, those whose disease was not surgically staged were found to significantly benefit from adjuvant chemo (OS HR, 1.75; 95% CI, 1.04 to 2.95). However in those optimally staged without evidence of metastatic disease, there was no benefit. This study was not powered to further analyze the influence of histology. Therefore, patients who do not have an optimal staging procedure should receive adjuvant chemotherapy. The benefit of adjuvant chemo in high-grade surgical stage I disease is unclear.

A literature review analyzed the results of 22 prospective randomized trials on the topic of benefit of adjuvant chemo in patients with early disease who had optimal surgical staging.[94] They concluded that adjuvant therapy is not advocated for patients with stage IA grade-1 tumors as their prognosis is excellent.[95] For patients with low-grade disease who did not have a comprehensive staging procedure, it is reasonable to offer completion of a staging procedure to avoid chemo in the proportion of patients shown to have no extra-ovarian disease. The alternative to avoid additional surgery is to give adjuvant chemo on the assumption that further disease is present in some patients.

Consideration of the prognostic factors (i.e., grade, stage, DNA ploidy, and CA 125 levels) may aid in assessing the probability of occult disease. For the clear cell subtype the acknowledged relative chemoresistance may suggest limited benefit from adjuvant chemotherapy.

Fertility-Sparing Therapy

Epithelial ovarian cancer occurs infrequently in women of childbearing age, with an estimated 8% of all malignant stage I epithelial cancers diagnosed in women younger than the age of 35.[96] Although there is relative consensus in regard to conservative surgical treatment (i.e., adnexectomy with comprehensive surgical staging), for patients with early-stage tumors of low malignant potential the literature is limited in regard to young patients with invasive epithelial tumors. Schilder et al[97,98] published a multiinstitutional study in 2002 on 52 women with stage IA ($n = 42$) or stage IC ($n = 10$) patients treated with fertility-sparing surgery and full surgical staging. Although all histologic cell types and grades were included, the majority of cases were mucinous ($n = 25$) and grade 1 ($n = 38$), and only 10 were of the serous cell type. Twenty patients received adjuvant chemo including all with stage IC grade 2 to grade 3. Five patients experienced relapse, and 2 died of their disease. The estimated 5-year OS was 98%, and the 10-year OS was 93%. Twenty-four patients, 6 who had received adjuvant chemo, attempted to conceive and 17 succeeded (71%). In a recent systematic review by Zapardiel et al, a total of 793 cases were reviewed and found to have a 5-year OS of 91%.[99] They further address the consensus in regard to fertility sparing in cases of stage I grade-1 and grade-2 ovarian cancer and the lack of consensus in regard to high-grade ovarian cancers. A study by Fruscio et al of 240 cases who underwent conservative treatment noted that although the tumor grade was the only independent predictor of poor prognosis the PFS and OS rates in the high-grade population is comparable to that shown in ICON1/ACTION trial where conservative treatment was not performed and therefore they conclude that conservative management does not seem to worsen prognosis.[100]

Young patients with stage IA disease can undergo fertility-sparing surgery and close follow-up without the need for adjuvant treatment. Patients with stage IC grade-2 to grade-3 disease can be managed with conservative surgery, but adjuvant chemo should be considered.

Radiation Therapy

Epithelial ovarian cancer is known to be a radiosensitive tumor. The benefit of adjuvant RT in patients with early-stage epithelial ovarian cancer has been evaluated in a series of studies.[101-103] Both intraperitoneal (IP) radioactive chromic phosphate suspension (^{32}P) and whole-abdomen irradiation (WAI) with a boost to the pelvis have been evaluated. Studies have suggested that the addition of RT to chemo for subsets of patients may have an expanding indication.[104-106]

Intraperitoneal Radioactive Chromic Phosphate Suspension (^{32}P)

Intraperitoneal instillation of radioisotopes, such as gold (^{198}Au) and chromic phosphate (^{32}P), have been studied in patients with ovarian cancer. It is now rarely used. Although the initial studies were performed using ^{198}Au, ^{32}P became the preferred isotope because of ease of handling, lack of gamma radiation, and a relatively low complication rate.[107] ^{32}P is a high-energy pure beta-particle emitter with a maximum energy of 1.71 MeV, a maximum penetration of 8 mm (average, 1 mm to 4 mm), and a half-life of 14.3 days. It can be used for intracavitary instillation at a dose of 10 mCi to 20 mCi. The majority of the ^{32}P is absorbed by the peritoneal surface via macrophages and then excreted through the lymphatic channels of the abdomen, that is, the thoracic lymphatics, and from there into the systemic vasculature where it is cleared by the liver. The retroperitoneal pelvic and paraaortic lymph nodes receive low doses of radiation. Because the main pattern of spread of ovarian cancer is transcoelomic, the IP instillation of radiocolloids, which deliver high doses of radiation to the peritoneal surfaces while minimizing systemic effect, would seem theoretically ideal. Gamma camera imaging of the abdomen has shown that the administration procedure including mobilization of the patients in the first 6 hours is critical for homogeneous dispersion of the radiocolloids on the serosal surfaces.[108] Dose calculations gave an estimated tissue surface dose of 30 Gy per 370 MBq of ^{32}P administered. The amount of ^{32}P in peripheral blood increased for 7 days after administration and was then followed by a continuous decrease. The estimated peripheral blood dose is 0.012 Gy, and the maximum bone marrow dose is 0.06 Gy.

TABLE 61-2 Early-Stage Ovarian Cancer: Randomized Trials of Whole-Abdomen Irradiation or ^{32}P

Trial/Author	Year	Stage	Study Design	No. Patients	5-Year Overall Survival (%)	Comments
NCIC/Klaassen[110]	1988	I, II	Pelvic RT + melphalan	106	61	^{32}P arm accrual closed early because of toxicity
			Pelvic RT + WAI	107	62	
			Pelvic RT + ^{32}P	44	66	
MDACC/Smith[103]	1975	I-III	WAI	51	71	<2 cm residual disease
			Melphalan	57	72	
PMH/Dembo[113]	1979	IB, II, III asymptomatic	WAI	76	64 (10-year)	$p = 0.007$
			Pelvic RT ± chlorambucil	71	40 (10-year)	
DACOVA/Sell[114]	1990	IB-IC, II	WAI	60	63 (4-year)	
			Pelvic RT + cyclophosphamide	58	65 (4-year)	
GOG 95/Young[51]	1990	IA-IBG3, IC, II	^{32}P	73	78	6% bowel obstruction in ^{32}P
			Melphalan	68	81	
NRH/Vergote[111]	1992	I-III	^{32}P or WAI	169	83	28 in ^{32}P arm treated with WAI
			Cisplatin	171	81	
GICOG/Bolis[112]	1995	IA-IB, IC	^{32}P	75	79	^{32}P not given in 20% of patients
			Cisplatin	77	81	
GOG 7602/Young[109]	2003	IA-IBG3, IC, II	^{32}P	110	78	3% bowel perforation in ^{32}P
			Cyclophosphamide + cisplatin	119	81	

Several randomized studies evaluating the efficacy of ^{32}P in early-stage ovarian cancer have been published[51,109-112] (Table 61-2). The earliest of the randomized trials was published in 1988 by the National Cancer Institute of Canada (NCIC).[110] Two hundred fifty-seven women with stages I to IIA high-risk ovarian cancer or with stage II disease were randomized to one of three trial arms: arm A, WAI (22.5 Gy in 20 fractions); arm B, melphalan; or arm C, ^{32}P. Surgical staging was not mandatory, and most patients' disease was not thoroughly staged. All patients were initially treated with pelvic RT (arm A: 22.5 Gy in 10 fractions; arms B and C: 45 Gy in 20 fractions). The ^{32}P trial arm was discontinued early because of increased bowel toxicity. No significant difference in survival was found.

In 1990 the Gynecologic Oncology Group (GOG) published a randomized controlled trial including 141 patients with stage I, grade-3 or stage II epithelial ovarian cancer randomly assigned to melphalan or a single dose of ^{32}P at the time of surgery.[51] With a median follow-up of more than 6 years the outcomes for the two treatment groups were similar with respect to 5-year disease-free survival (DFS) (80% in both groups) and 5-year OS (81% with melphalan versus 78% with ^{32}P; $p = 0.48$). They concluded that either treatment was a reasonable option.

In 1992, Vergote et al[111] published a randomized trial of 347 patients, stages I to III (no gross residual tumor), who were allocated to cisplatin (50 mg/m^2) every 3 weeks for six cycles or ^{32}P. Patients with intraabdominal adhesions allocated to IP administration of ^{32}P were treated with WAI (22 Gy to the whole abdomen in 20 fractions) followed by 22 Gy in 11 fractions to the pelvis. Patients did not undergo comprehensive staging because lymph node sampling was not performed. The estimated 5-year OS of patients with stage I disease were 82% for the ^{32}P arm, 94% for the WAI arm, and 79% for the cisplatin arm ($p = 0.79$, $p = 0.44$ compared with the cisplatin arm, respectively). Bowel obstruction occurred more frequently in those treated with ^{32}P (9%, $p = 0.02$) or WAI (21%, $p = 0.001$) in comparison with the cisplatin arm (2%). Because no survival benefit was shown, cisplatin was recommended as the standard treatment.

The Italian Gruppo Interregionale Collaborativo in Ginecologia Oncologica (GICOG) performed a randomized trial[112] of 152 women with stage IA grade 2, IB grade 2, and IC disease, comparing treatment with cisplatin with that with ^{32}P. Patients underwent a surgical procedure that did not include lymph node sampling. In 15 patients randomized to treatment with ^{32}P, the radioisotope was not delivered, owing to the development of abdominal adhesions. An improved 5-year PFS was reported for the cisplatin group in comparison with the ^{32}P group (85% versus 65%, $p = 0.008$) but without an OS difference (81% versus 79%, $p = 0.35$).

The latest randomized study was published by the GOG in 2003. Two hundred twenty-nine women with early-stage ovarian cancer at high risk for relapse (defined as stage IA or IB grade 3, stage IC, or stage II, no macroscopic residual) were assigned to treatment with ^{32}P or with cyclophosphamide and cisplatin.[109] The cumulative incidence of relapse at 10 years was 35% for the ^{32}P arm and 28% for the cyclophosphamide-cisplatin arm. Patients receiving cyclophosphamide-cisplatin had a relapse rate 29% lower than those in the RT arm ($p = 0.15$) and a death rate 17% lower than those in the RT arm ($p = 0.43$). The toxicity profiles of both regimens were reasonably well tolerated, although 3% of the patients receiving ^{32}P suffered perforation of the small bowel during the insertion of the IP catheter and 7% had problems with inadequate distribution. Grade-3 or grade-4 gastrointestinal toxicity was seen in 12% of patients treated with cyclophosphamide and cisplatin. The authors concluded that, although there were no statistically significant differences, the lower relapse rate seen in the chemo arm together with ^{32}P complications make platinum-based chemo the preferred adjuvant therapy.

External Beam Irradiation

WAI has generally been used in patients in whom the tumor was completely resected or in whom macroscopic disease is

<2 cm in diameter and located only in the pelvis. Adjuvant WAI has generally not been used to treat macroscopic extrapelvic residual disease because tolerable doses of radiation are generally insufficient to eradicate more than microscopic residuum except in the pelvis, where higher doses may be administered. Its advantage in comparison to ^{32}P is the ability to deliver a homogeneous dose to all areas of the abdomen and pelvis and the ability to encompass the pelvic and paraaortic lymph nodes. The disadvantage of WAI with conventional techniques is the dose-limiting acute and late toxicity related to the treatment, which is predominantly hematologic and gastrointestinal. The target volume includes the entire peritoneum, with the cephalad border being superior to the diaphragm and the caudal border the pelvic floor, thus encompassing peritoneal surfaces, pelvic and paraaortic lymph nodes, and the organs in the abdomen and pelvis. As the majority of relapses are confined to the abdominal and pelvic cavity, it is reasonable to expect that RT techniques that encompass the entire peritoneal cavity would be more likely to be curative. The total dose to the whole abdomen is limited to 25 Gy to 30 Gy, owing to the dose-limiting organs in the field, although the pelvis is usually given a total dose of 45 Gy.

Multiple randomized trials have been published evaluating the efficacy and toxicity of WAI in patients with early-stage ovarian cancer (see Table 61-2). Early studies established the inadequacy of treating the pelvis alone in patients with no gross residual disease.[113,115,116]

A trial from the Princess Margaret Hospital randomized 147 women with stages I to III disease comparing WAI and pelvic RT to pelvic RT alone or in combination with chlorambucil.[113] After a 7-year follow-up, the 10-year OS difference was significantly higher in the 76 patients treated with pelvic and WAI in comparison to the 71 patients treated with pelvic RT and chlorambucil (46% versus 31%, $p = 0.05$). The survival benefit was present only in patients with no gross residual disease or small volume pelvic residuum (<2 cm).

Hreshchyshyn et al[117] published a randomized trial of 86 patients who were clinical stage I (not surgically staged) randomized to pelvic RT, melphalan, or no additional treatment. They did not find a survival difference between observation and pelvic RT but did find a benefit for melphalan.

Several studies have compared chemo to RT, although only one incorporated a cisplatin-based regimen.[110,114,118,119] As previously noted, the NCIC randomized 257 women with stage I, IIA high-risk ovarian cancer, or stage IIB, and stage III to one of three trial arms: whole-abdomen/pelvic RT, melphalan, or ^{32}P.[110] No significant difference in survival was found. Smith et al[97] randomly assigned 149 patients with early-stage ovarian cancer to postoperative whole-abdomen/pelvic RT or melphalan. No survival difference was found between the groups.

The Northwest Oncologic Cooperative Group of Italy (NOCGI) conducted the only prospective randomized trial[119] in women with high-risk early-stage (stage I or II) ovarian cancer, comparing WAI with a cisplatin-based regimen. It was not completed. They randomized 70 women to cisplatin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 or to WAI in an open technique, consisting of 43.2 Gy/24 fractions to the pelvis and 30.2 Gy to the upper abdomen. The study was closed early owing to multiple protocol violations (63% of patients were treated with chemo) and low accrual. With a median follow-up of 60 months, the 5-year OS was 71% for the cisplatin and cyclophosphamide arm and 53% for the WAI arm ($p = 0.16$). Although toxicity was well tolerated in the chemo arm of the study, in the WAI arm 28% of patients suffered from grade-3 to grade-4 acute diarrhea, two had severe enteritis requiring hospitalization, and one had late bowel obstruction requiring surgery.

In 1996, the GOG initiated a prospective randomized trial comparing WAI with platinum-based chemotherapy. Unfortunately the trial was not completed because of low accrual rates.

In the majority of studies looking at the efficacy of RT, all epithelial malignancies were included. There is some suggestion that certain histologic subtypes might benefit from the use of RT. Clear cell carcinomas particularly are typically chemotherapy resistant. Small studies have been conducted. Nagai et al[105] compared adjuvant platinum-based chemo to adjuvant WAI alone in 28 women with stages I to III ovarian clear cell carcinoma. Five-year OS and DFS in the RT arm were 81.8% and 81.2% versus 33.3% and 25% in the chemo arm ($p = 0.031$, $p = 0.006$), respectively. Locoregional control was also considerably improved with adjuvant RT. Only 1 of the 16 patients receiving RT had an isolated locoregional recurrence versus 7 who had locoregional recurrences in the 12 patients in the chemo arm. Dinniwell et al[104] performed a prospective, risk-stratified study of 29 patients with stages I to III epithelial ovarian cancer combining surgery, chemo, and adjuvant WAI. The subset of 11 patients with clear cell carcinoma and 5 with endometrioid histologies showed the greatest gains from this aggressive, multimodality approach, with a 4-year DFS of 77% compared with 27% for serous subtypes ($p = 0.01$). Finally, a retrospective but hypothesis generating study by Swenerton et al reported an improved survival in patients with stages I and II clear cell, endometrioid, and mucinous histotypes with the addition of adjuvant WAI to chemotherapy.[106] This group further published in 2012 a study on 241 stages I to II clear cell ovarian cancers comparing two groups; those treated with adjuvant chemo and RT and those treated with chemo only.[120] By physician choice, 211 were treated with chemo alone and 103 had the addition of pelvic and whole abdominal RT in a dose of 22.5 Gy to the pelvis in 10 fractions, followed by 22.5 Gy in 22 fractions to the whole abdomen. Although the groups were not randomly assigned, the stage distribution was comparable between the groups. They found no benefit for radiation in patients with stages IA and IC (rupture alone); however, a PFS benefit of 20% at 5 years in patients with stage IC and stage II was observed. For patients wit stage IC disease (cytology positive or surface involvement) this represents a RR reduction of 49% in those treated with radiation in comparison to those treated with chemo alone. The hypothesis generated from this observation was that improved pelvic control translated into a lower rate of relapse in this patient population. At this point in time there is limited data however. Given that clear cell cancers often are pelvic confined and that they are chemo resistant, an innovative research approach might consider examining a combination of novel targeting agents and pelvic RT in nonserous subtypes.

The trials cited in this section have demonstrated that radiation is an effective adjuvant modality for specific patients with ovarian cancer. However, currently it is used rarely and platinum-based chemo is considered the preferred modality. The role of adjuvant RT in certain early-stage nonserous histologies should be investigated.

LOCALLY ADVANCED DISEASE AND PALLIATION

Advanced-Stage Disease

The majority of cases of epithelial ovarian cancer are diagnosed when the tumor has spread throughout the abdomen and pelvis. Exploratory laparotomy is performed for the purpose of diagnosis, staging, and treatment.

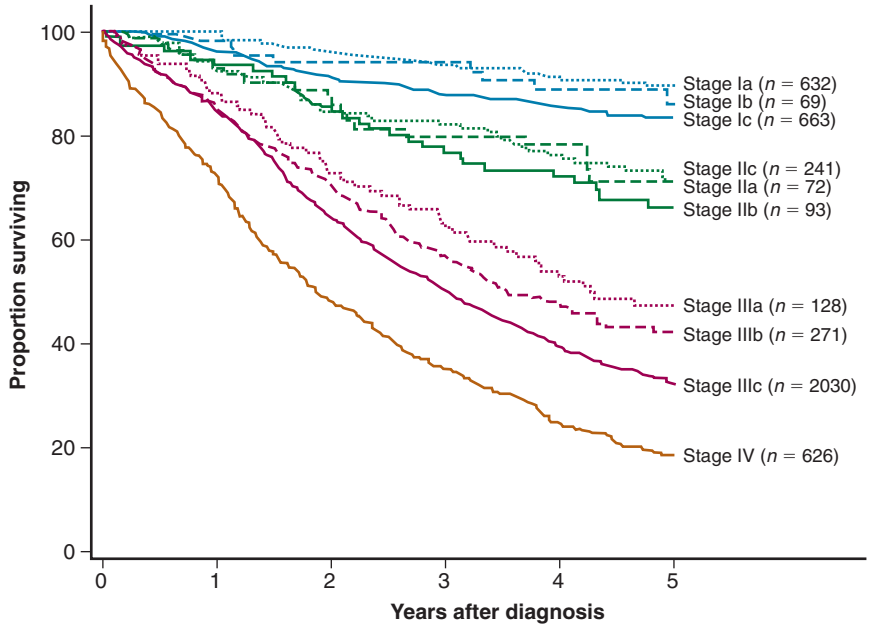
Epithelial ovarian cancer predominantly spreads throughout the peritoneal cavity and multiple masses are regularly

found at time of exploration. For most solid tumors, aggressive surgical resection is justified only if all known tumor can be excised; however, in ovarian cancer this is not the case. Cytoreductive surgery (known also as "debulking") is the standard. Munnell et al[121] were the first to introduce the concept of "maximum surgical effort" for ovarian cancer in 1968. They report on improved survival when patients had a maximum surgical effort in comparison to a biopsy or partial removal. Griffiths[122] was the first to show a significantly improved survival from this strategy in patients with residual disease less than 1.5 cm. Since then, "optimal debulking" has been defined as no tumor masses larger than 1 cm at the completion of surgery; however, the outcome is superior when there is no macroscopic residual.[123]

Hoskins et al reported on the effect of the maximum size of residual disease on the prognosis.[124] They found that among patients with suboptimal debulking (>1 cm residual disease), those with small-diameter residual disease (<2 cm) tended to survive longer than those who had larger residual disease. However, among those with larger residual disease, size did not affect prognosis appreciably. In 2006, Heintz et al[125] published an annual report on ovarian cancer. Five-year OS for the 2160 patients diagnosed with stage IIIC disease was 62.1% for no macroscopic, 32.9% for size less than 2 cm, and 24.8% for size greater than 2 cm. In concordance with the findings of Hoskins et al,[124] the most significant difference is between no macroscopic disease and any macroscopic residual disease (Figures 61-2 and 61-3).

These findings are important to guide management. Therefore, if disease cannot be cytoreduced to less than 2 cm, there is no survival advantage in proceeding with the debulking surgery, which can be a morbid procedure, especially if bowel resections, liver resections, and ostomies are added.

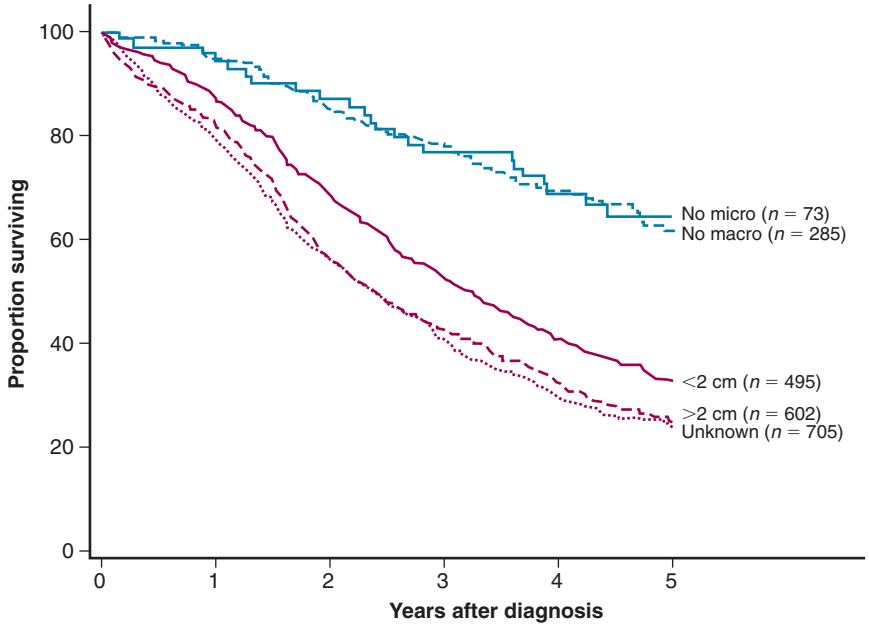
Patients presenting with stage IV disease have been included in most advanced ovarian cancer studies; precise data on their benefit from cytoreductive surgery are limited. Similar to the findings in stage III disease, retrospective studies have shown a statistically significant improvement in survival in cases in which optimal debulking is achieved.[126,127] Bristow et al[126] found optimal surgical debulking and performance status to be important determinants of survival. They showed that even in patients with unresectable liver metastasis,



Stage	Patients (*n*)	Mean age (yr)	Overall survival (%) 1-yr	2-yr	3-yr	4-yr	5-yr	Hazards ratio[a] (95% CI)
Ia	632	53.5	98.4	96.2	93.5	91.1	89.6	Reference
Ib	69	54.1	100.0	93.9	93.9	88.6	86.1	0.8 (0.4–1.6)
Ic	663	52.8	96.3	91.4	87.9	85.6	83.4	1.1 (0.8–1.4)
IIa	72	56.1	93.0	87.2	79.7	78.1	70.7	1.8 (1.1–3.0)
IIb	93	57.4	93.4	84.5	76.6	71.9	65.5	2.1 (1.4–3.1)
IIc	241	56.3	93.6	85.6	82.3	75.8	71.4	1.8 (1.4–2.5)
IIIa	128	57.1	88.1	72.6	63.1	52.8	46.7	4.0 (2.9–5.4)
IIIb	271	58.2	85.7	70.6	56.8	47.7	41.5	4.4 (3.4–5.7)
IIIc	2030	59.7	84.8	64.5	50.3	39.3	32.5	5.8 (4.7–7.0)
IV	626	60.4	72.4	48.4	35.2	24.8	18.6	8.9 (7.2–11.0)

[a]Hazards ratio and 95% confidence intervals obtained from a Cox model adjusted for age and country.

Figure 61-2 Stage and prognosis and residual disease and prognosis. Carcinoma of the ovary: patients treated from 1999 to 2001. Survival by FIGO stage, obviously malignant, *n* = 4825.
Data from Heintz AP, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO 6th annual report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 95(Suppl 1):S161–S192, 2006.



Residual disease	Patients (*n*)	Mean age (yr)	Overall survival (%) 1-yr	2-yr	3-yr	4-yr	5-yr	Hazards ratio[a] (95% CI)
No micro residual	73	55.8	94.4	87.1	76.8	68.6	63.5	Reference
No macro residual	285	56.3	95.0	85.0	77.9	69.3	62.1	1.0 (0.6–1.6)
≤2 cm	495	58.9	86.8	68.7	52.3	40.8	32.9	2.3 (1.5–3.5)
>2 cm	602	60.6	82.0	56.4	42.6	32.0	24.8	3.0 (1.9–4.5)
Unknown	705	61.1	79.6	56.3	40.7	29.3	24.1	2.9 (1.9–4.5)

[a]Hazards ratio and 95% confidence intervals obtained from a Cox model adjusted for age, stage and country.

Figure 61-3 Carcinoma of the ovary: Patients treated from 1999 to 2001. Survival in patients with stage IIIc disease by completeness of surgery, *n* = 2160.
Data from Heintz AP, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO 6th annual report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 95(Suppl 1):S161–S192, 2006.

optimal debulking of extrahepatic disease is associated with a significant survival advantage.

The success rate for optimal debulking varies widely between studies, from 20% to 85%.[128-130] This can be attributed to many factors, including the definition of optimal debulking, the expertise of the surgeon, the patient population (the percent of patients deemed unresectable before a surgical attempt), and probably the biology of the disease.

Because many patients cannot be optimally debulked initially, or the procedure needed to accomplish this is associated with a high risk of significant morbidity, neoadjuvant chemo to accomplish debulking has been introduced and studied. Several retrospective studies have reported survival results of patients treated with neoadjuvant chemo followed by interval debulking to be the same as for patients treated with primary debulking surgery.[131-134]

In the 1980s the European Organization for Research and Treatment of Cancer (EORTC) and the GOG (protocol 152) initiated two randomized trials to investigate the role of interval debulking in cases in which optimal debulking cannot be achieved at primary surgery.[135,136] The EORTC study included 278 women with suboptimally debulked disease (>1 cm residuum, FIGO stages IIB to IV). After completing three cycles of chemo (cisplatin-cyclophosphamide), the patients were randomized to an additional three cycles of chemo or to interval debulking followed by three more cycles of chemotherapy. The 2-year PFS and OS were significantly higher in the interval-debulking arm (OS, 56% versus 46%, $p = 0.01$). The difference in median OS was 6 months. After adjusting for other prognostic factors, interval debulking reduced the risk of death by 33%. GOG protocol 152 randomized 425 suboptimally debulked patients (>1 cm residual disease) who received three cycles of paclitaxel and cisplatin plus interval debulking (followed by three additional cycles of chemo) or three further cycles of chemo without surgery.[136] The median survival and PFS of the two groups was similar (32 versus 33 months and 10.5 versus 10.8 months, respectively). Their conclusion was that women who underwent an initial maximal but suboptimal debulking procedure did not benefit from interval debulking surgery. One of the main differences between the trials was that the initial surgery in protocol 152 was required to be appropriate ovarian cancer surgery (the majority performed by a gynecologic oncologist), whereas in the EORTC trial many of the patients had a minimal surgical effort at primary surgery by a general gynecologist. The majority consensus from these two studies is that debulking surgery should be performed by a gynecologic oncologist.[137]

Bristow and Chi[134] performed a meta-analysis including 22 studies. They concluded that neoadjuvant chemo is correlated with a worse prognosis than primary debulking surgery. The EORTC in collaboration with the NCIC in 2010 published the results of a prospective randomized trial including 718 patients with stages IIIC to IV ovarian cancer randomized to primary debulking surgery and six cycles of postoperative chemo or

to three cycles of neoadjuvant chemo followed by interval debulking and an additional three cycles of chemotherapy.[138] The results show a HR for death (intention-to-treat analysis) of 0.98 (90% CI, 0.84 to 1.13; $p = 0.01$ for noninferiority), and the HR for progressive disease of 1.01 (90% CI, 0.89 to 1.15) with a median PFS of 12 months in both groups. Complete resection of all macroscopic disease at surgery was the strongest independent variable in predicting OS. Importantly significant reduction in surgical complications in the interval debulking arm, including postoperative deaths (2.5% versus 0.7%), was noted. The results of this multiinstitution, multinational trial were not universally accepted. The rate of complete cytoreduction at primary surgery was low (19.4%) and remarkably variable with a range of 3.9% to 62.9%. This suggests a lack of surgical expertise and begs the question of generalizability of the results to centers with high surgical standards. In addition the survival of patients who underwent primary debulking was considered modest in comparison to other previous publications of nonrandomized data. Hence, in advanced stage ovarian cancer the decision between neoadjuvant chemo and interval debulking versus primary debulking surgery is still controversial.

Role of Chemotherapy

Surgery alone is not curative for advanced-stage ovarian cancer as microscopic residual disease is inevitable. Epithelial ovarian cancer is highly chemosensitive; therefore, standard postoperative treatment is combination chemotherapy. Platinum compounds are the most active agents and are the foundation of treatment. Their first use was reported in a small trial in 1982, which suggested a possible benefit to the addition of cisplatin to cyclophosphamide.

In 1986, the GOG published a randomized trial of 440 patients with advanced-stage ovarian cancer, comparing cyclophosphamide and doxorubicin with or without cisplatin.[139] The clinical complete response rate was 26% for cyclophosphamide and doxorubicin and 51% for the combination of cyclophosphamide, doxorubicin, and cisplatin ($p = 0.0001$). A survival benefit was seen for the platinum-based regimen in patients with measurable disease (median OS, 19.7 versus 15.7 months, $p < 0.03$), although not for patients without measurable disease. This and other trials lead to the use of platinum-based combination regimens as the standard of care. One of the important advances made in chemotherapeutic treatment of advanced ovarian cancer is the incorporation of the taxane, paclitaxel, into combination regimens. The GOG performed a randomized trial (protocol 111) comparing therapy with cisplatin and paclitaxel to that with cisplatin and cyclophosphamide.[140] Three hundred eighty-six suboptimally debulked (residual tumor > 1 cm) patients were randomized. Of the 216 with measurable disease, a superior response rate and survival was found for the cisplatin-paclitaxel trial arm (73% versus 60%, $p = 0.01$ and median OS, 38 versus 24 months, $p < 0.001$), respectively. The EORTC-NCIC performed an intergroup trial (OV-10) recruiting 680 women with broader inclusion criteria.[141] They included patients with stages IIB and IIC disease and optimal residuum and allowed for interval debulking. The overall response rate, PFS, and OS were statistically improved in the cisplatin-paclitaxel trial arm with median prolongation in OS of 10 months (35.6 versus 25.8 months, $p = 0.0016$). After the publication of these two Phase III randomized trials, the use of cisplatin-paclitaxel was established as the new standard of care.

Carboplatin, a second-generation platinum-based agent, is less nephrotoxic, neurotoxic, ototoxic, and emetogenic in comparison with cisplatin, although it is associated with a higher degree of myelosuppression, primarily thrombocytopenia.[142-144] Because of its renal excretion, patients with impaired renal function require individualized dose adjustment.[142] Multiple studies have shown equivalent efficacy between cisplatin and carboplatin and less toxicity for the latter. A meta-analysis of 12 randomized trials, including 2219 patients and 1745 deaths, confirmed this whether given as a single-agent or in combination regimens.[143]

The GOG performed a Phase III, noninferiority trial (protocol 158) of 792 women with small-volume stage III disease comparing cisplatin-paclitaxel and carboplatin-paclitaxel.[144] Median OS was 48.7 months for patients receiving cisplatin-paclitaxel arm compared with 57.4 months for those with carboplatin. The RR of death was 0.84 (95% CI = 0.70 to 1.02) for the carboplatin plus paclitaxel group. The GOG concluded that carboplatin plus paclitaxel resulted in less toxicity (gastrointestinal, renal, and grade-4 leukopenia) and was not inferior when compared with cisplatin plus paclitaxel. Combined therapy with carboplatin and paclitaxel is now considered the standard for first-line care of epithelial ovarian cancer.

The Gynecologic Cancer Intergroup (GCIG) evaluated the benefits of incorporating an additional cytotoxic drug or doublet with carboplatin-paclitaxel.[145] Women with stages III and IV epithelial ovarian cancer ($n = 4312$) were randomized to one of five trial arms (incorporating gemcitabine, liposomal doxorubicin, and topotecan) and compared to carboplatin-paclitaxel. There were no improvements in PFS or OS for the experimental regimens. Thus, the addition of these specific third chemotherapeutic drugs to the carboplatin-paclitaxel combination is not indicated.

Dose intensity of platinum regimens has been evaluated in numerous studies of different regimens.[146-148] There appears little evidence to support increased dose intensity of cisplatin and cyclophosphamide in regimens for advanced-stage epithelial ovarian cancer.[146] In 2009 Katsumata et al reported on a Phase III randomized controlled open label trial (JGOG 3016) of 637 patients with stages II to IV ovarian, fallopian tube or primary peritoneal cancer comparing a conventional regimen of six cycles of paclitaxel (180 mg/m^2; 3-hour IV infusion) plus carboplatin (AUC 6), given every 21-days to a dose-dense paclitaxel regimen (80 mg/m^2; 1-hour IV infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle.[149] They demonstrated a statistically significant improvement in median PFS (28 versus 17.2 months; HR, 0.71; 95% CI, 0.58 to 0.88) and 3-year OS (72.1% versus 65.1%; HR, 0.75; 95% CI, 0.57 to 0.98) for those who received the dose-dense regimen. Furthermore, in a subsequent publication looking at long-term results at a median follow-up of 6.5 years they reported a median OS of 100.5 months in the dose-dense treatment group and 62.2 months in the conventional treatment group (HR, 0.79; 95% CI, 0.63 to 0.99; $p = 0.039$).[150] Two large confirmatory trials of dose dense paclitaxel are under way: GOG 262 has completed accrual and results should be available soon and ICON8 completed accrual in the fall of 2014.

IP chemo has been evaluated in three large Phase III randomized trials.[151-153] Alberts et al published in 1996, a Phase III trial of IP cisplatin and IV cyclophosphamide compared with IV cisplatin and IV cyclophosphamide in 546 women with stage III optimally debulked (residual disease <2 cm) ovarian cancer.[152] Outcomes were improved for the IP arm and had less toxicity. However, because cyclophosphamide was no longer a standard regimen, additional studies were required to determine if the advantage was related to the route of administration when regimens incorporating paclitaxel were given.

In 2006, the GOG published a Phase III randomized trial (protocol 172) comparing IP cisplatin and paclitaxel compared with IV cisplatin and paclitaxel.[153] The median OS was found to be 49.7 months in the IV chemo arm and 65.6 months in the IP arm ($p = 0.03$). However, only 42% of patients allocated to

IP chemo completed all six IP cycles (primarily because of catheter-related issues and toxicity), in comparison to 83% allocated to IV chemotherapy. All patients who could not complete treatment in the allocated trial arm were switched to intravenous carboplatin. Quality of life was found to be significantly worse in the IP trial arm up to 6 weeks after treatment but returned to being equivalent to the IV arm 1 year after treatment.[154]

A systemic review of IP chemo identified seven randomized trials: three large Phase III trials and four smaller randomized trials.[155] All three large trials detected a statistically significant benefit in OS with IP cisplatin-based chemotherapy. A pooled analysis of six of the trials confirmed a survival benefit with IP cisplatin-based chemo (RR, 0.88; 95% CI, 0.81 to 0.95). Significant adverse effects including catheter-related complications were more common in the IP group.

In 2006 the U.S. National Cancer Institute (NCI) issued a clinical announcement advocating the use of IP chemo in the treatment of women with optimally debulked ovarian cancer.[156] Although the trials of IP chemo show a survival advantage, the incorporation of IP therapy into general practice is low. The reasons for the reluctance of practitioners include the high level of toxicity associated with the specific regimens showing benefit, the technical difficulties in delivery of the treatment, particularly the necessity for catheter placement and management, and the fact that no trial to date has compared IP chemo with the standard IV carboplatin-paclitaxel. Those using IP chemotherapy usually use lower doses than those reported in the positive trials. The GOG is currently performing trials of IP carboplatin-paclitaxel.

The majority of patients with ovarian cancer enter a state of remission on completion of surgery and postoperative chemotherapy. However, approximately 85% of patients in remission ultimately experience relapse; therefore, maintenance therapy has been proposed and investigated.

A GOG study (GOG 178) evaluated the efficacy of 12 versus 3 cycles of maintenance paclitaxel in patients who achieved a complete response to primary chemotherapy.[157] Because of an improvement in PFS with 12 cycles on an interim analysis (28 months versus 21 months, $p = 0.035$), the trial was closed. It was recommended that all participants then receive 12 cycles of paclitaxel. The difference in PFS did not translate into an OS benefit (median OS 53 versus 48 months for patients who received 12 versus 3 cycles of maintenance paclitaxel [$p = 0.34$]).[158] The proposed explanations behind the improved PFS without an improved OS include the high efficacy of treatment at relapse, crossover into the 12-cycle arm, and an insufficient sample size.

Currently, maintenance therapy with conventional antineoplastic agents is not recommended.

Molecular Targeting Agents

Molecular-targeted therapies have become the frontline of cancer research in many tumor sites and their investigation in ovarian cancer has evolved in the last 5 years. Two Phase III trials (GOG-0218 and ICON7) have evaluated the role of bevacizumab as concomitant and maintenance therapy in first-line therapy for ovarian, fallopian tube, and primary peritoneal cancers following surgical cytoreduction.[159,160] GOG 218, a double-blind, placebo-controlled Phase III randomized trial of 1873 stage III (incompletely resectable) or patients with stage IV ovarian cancer randomized to one of three arms; standard chemotherapy with placebo from cycles 2 through 22, standard chemotherapy with bevacizumab (15 mg/kg of body weight) from cycles 2 through 22 and standard chemotherapy with bevacizumab from cycles 2 through 6 and then placebo during cycles 7 through 22.[159] No difference in PFS was found between the control group and the arm treated with concomitant bevacizumab; however, a statistically significant increase in PFS was found between the control arm and the treatment arm of maintenance bevacizumab (10.3 months versus 14.1 months), with a HR of progression or death of 0.717 (95% CI, 0.625 to 0.824). No OS or quality-of-life differences were found between the three arms. Hypertension grade-2 or greater was more common with bevacizumab than with the placebo in a cost effectiveness evaluation by GOG. Because of the high drug cost, bevacizumab was not cost effective.[161] ICON7, a double-blind, placebo-controlled Phase II study, randomly assigned 1528 women after initial surgery to standard chemotherapy plus placebo or standard chemotherapy and bevacizumab (7.5 mg/kg for 6 cycles), followed by bevacizumab alone for an additional 12 cycles. The patient population in ICON7 differed from GOG 218 and included patients with early (9%) and advanced stage (70% had stage IIIC or IV) disease; 9% of patients had early-stage and 26% had residual tumor larger than 1 cm at completion of surgery. Median PFS was 17.3 months in the control group and 19 months in the group receiving bevacizumab. HR for progression or death in the bevacizumab group was 0.81 (95% CI, 0.70 to 0.94). There were more side effects in the bevacizumab arm including hypertension, thromboembolic events, and gastrointestinal perforations; however, no difference in quality of life was found. Both trials showed a modest increase in PFS with maintenance bevacizumab but no difference in OS or quality of life.

Additional molecular targeted treatments are currently under development for specific populations including a Phase III trial of maintenance poly ADP ribose polymerase (PARP) inhibitor in *BRCA* mutation carriers. The role of various novel molecular-targeted therapies in the adjuvant and the recurrent setting is an important question that needs to be addressed in the next decade. Careful cost-effective and patient-reported outcomes need to be incorporated into trial designs.

Role of Radiation Therapy

The role of "consolidation" RT in ovarian cancer as sequential to surgery and chemotherapy is controversial. Several publications have addressed the benefit of RT in multiple scenarios, although the limitations of the studies have made definitive conclusions difficult. Dembo et al[113] previously showed that WAI is an effective treatment of small residual tumor (<2 cm); therefore it seemed reasonable to suggest that there could be a benefit from administering WAI for consolidative treatment. In 1982 Fuks et al[162] proposed a new paradigm of treatment for stage III ovarian cancer, including initial surgery followed by aggressive combination chemotherapy, second-look laparotomy (to include cytoreduction), followed by WAI.

Several Phase III studies have since evaluated the efficacy of this multimodality treatment paradigm in comparison to postoperative extended chemotherapy (Table 61-3). Bruzzone et al[163] randomized 41 patients with no or minimal disease (<2 cm) at second-look laparotomy to an additional three cycles of platinum-based chemotherapy or WAI (total dose was 43.2 Gy/24 fractions to the pelvis and 30.2 Gy to the upper abdomen). Median survival and PFS were found to be 24 months and 16 months, respectively, in the patients in the RT arm of the study. In the chemotherapy arm, median survival and PFS were not reached at the time of publication. The trial was closed early owing to the superior survival of the patients treated with chemotherapy. In 1993 the North Thames Ovary Group study (NTOG)[164] randomized 117 patients with advanced ovarian cancer (stages IIB to IV) who had received postoperative carboplatin and were found to have minimal residual disease at second-look laparotomy to an additional five courses of carboplatin or WAI (24 Gy). No statistical difference was found in either DFS or OS between the groups.

TABLE 61-3 Randomized Trials of Consolidative WAI or ^{32}P

Trial/Author	Stage	Study Design	No. Patients	5-Year Overall Survival (%)	Bowel Obstruction
West Midlands/Lawton[165]	IIB residual, III, IV	WAI Chlorambucil	56 53	7 8	9%
Italy/Bruzzone[163]	III, IV minimal residual disease	WAI Chemotherapy	20 21	45 (3-year) 85 (3-year)	5%
NTOG/Lambert[164]	IIB-IV <2 cm residual disease	WAI Carboplatin	58 59	25 30	1.7%
Sweden-Norway/Sorbe[166]	III	WAI Cisplatin + doxorubicin/epirubicin Observation	32 35 31	56 (PFS) 36 (PFS) 36 (PFS)	10%
Germany/Pickel[167]	IC-IV no clinical disease	WAI Observation	32 32	59 33	3.1%
NRH/Vergote[168]	IAG2-3, IB, III	^{32}P Observation	25 25	95 (PFS) 82 (PFS)	4%
GOG 93/Varia[169]	III	^{32}P Observation	104 98	67 63	2.9%

PFS, *Progression-free survival;* WAI, *whole abdomen irradiation.*

Additional studies have shown mixed results when estimating a survival benefit for consolidation WAI.[165,170] Thomas[171] published a review in 1993 on the role for consolidation or salvage RT in advanced epithelial ovarian cancer. Twenty-eight studies with 713 patients were included. Overall, the evidence did not support an incremental curative benefit for WAI; however, because of the diverse inclusion criteria and the limited amount of patients in each trial, a decisive conclusion could not be made.

Two randomized trials published subsequent to this review have shown relatively optimistic results.[166,167] Pickel et al[167] performed a randomized study of 64 patients with stages IC to IV disease but without evidence of clinical disease after comprehensive surgical staging and platinum-based chemotherapy comparing WAI versus no further treatment. The 5-year DFS and OS of the patients who received WAI was significantly higher than those who were observed (49% versus 26%, $p = 0.13$, and 59% versus 33%, $p = 0.029$, respectively). This benefit was more obvious in patients with stage III disease (5-year OS, 59% versus 26%, $p = 0.012$). In 2003, group collaboration from Sweden and Norway published a randomized trial comparing consolidation treatment with RT or chemotherapy versus observation in 172 patients with stage III disease who underwent cytoreductive surgery and four cycles of platinum-based chemotherapy followed by second-look surgery.[166] Only patients with no macroscopic disease were included; patients with microscopic disease were randomized to chemotherapy or WAI, and patients with no microscopic disease were randomized to chemotherapy, WAI, or observation. Consolidation RT was a significant ($p = 0.050$) prognostic factor with regard to PFS in the subgroup with complete pathologic remission. In the subgroup with microscopic residual carcinoma, no differential benefit for RT or chemotherapy was observed. Late complications in the RT arm included four cases as grade 1 (diarrhea) and seven cases (10%) as grade 3 (intestinal obstruction).

Consolidative Intraperitoneal Radioactive Chromic Phosphate Suspension (^{32}P)

The role of ^{32}P as consolidative treatment after surgery and chemotherapy in advanced-stage ovarian cancer has been evaluated in several studies (see Table 61-3). The largest retrospective study from the University of North Carolina evaluated ^{32}P in 51 women with stages I to III disease.[172] They treated patients with no evidence of disease on second-look laparotomy with 15 mCi of ^{32}P. These patients were compared with 18 patients who had a negative second-look laparotomy but did not receive ^{32}P because of peritoneal adhesions, other protocols, or physicians' preference; with 15 who did not receive any additional treatment; and with 3 who received additional chemotherapy. After a median follow-up of 58 months, both an improved 5-year PFS (86% versus 67%, $p = 0.05$) and a 5-year OS (90% versus 78%) were noted in the ^{32}P group.

Two randomized trials of ^{32}P have been published.[168,169] The first was performed at the Norwegian Radium Hospital in which 50 patients with stage IA high-grade and stages IB to III disease were randomized after a negative second-look laparotomy to ^{32}P or no further treatment.[168] No significant survival difference was found between the groups; however, ^{32}P was associated with a considerable number of bowel complications. In 2003 the GOG (protocol 93) reported on a prospective randomized trial of 202 patients with stage III disease with a negative second-look laparotomy who were allocated to 15 mCi of ^{32}P or no further treatment.[169] After a median follow-up of 63 months, 5-year OS was 67% and 63% for IP ^{32}P and no further treatment groups, respectively. No significant difference in PFS or OS was found between the study arms. Three patients in the ^{32}P arm required surgery because of bowel obstruction. Thus, the data do not support the use of ^{32}P for consolidative treatment in ovarian cancer.

Recurrent Ovarian Cancer

Approximately 85% of patients with epithelial ovarian cancer will experience relapse. Recurrent or persistent ovarian cancer after first-line therapy is almost always incurable. The majority of the relapses (85%) are in the abdomen alone. Bowel symptoms are common. Treatment is generally aimed at prolonging symptom-free survival and palliating symptoms.

Patients with recurrent ovarian cancer are categorized by their "platinum sensitivity," which is primarily defined by the length of the treatment-free interval. Patients whose disease progresses during therapy or who experience a relapse less than 6 months from the completion of treatment are generally referred to as "platinum resistant," and their response rates and survival tend to be low and short. Patients presenting with early relapse are considered for second-line chemo

regimens or clinical trials. Many second-line chemo agents have been evaluated (liposomal doxorubicin, gemcitabine, topotecan, paclitaxel, and others), with response rates on the order of 10% to 15%.[173-176] In these patients, the median PFS is 3 months to 4 months and the median OS is 9 months to 12 months. Preliminary results of AURELIA, the first Phase III randomized trial of chemo with or without bevacizumab in patients with recurrent platinum-resistant ovarian cancer were presented in 2012.[177] The standard chemo group had an expected 12.6% response rate, whereas the response rate in the bevacizumab arm was significantly improved when measured by CA125 levels or RECIST criteria. Median PFS was 3.4 months in the control arm and 6.7 months in the bevicizumab arm ($p < 0.001$). The final results are pending. Other molecular targeting agents continue to be explored in recurrent, platinum-resistant disease. Because the chance of a meaningful disease-free interval is low, quality of life, treatment-related toxicity, and the patient's wishes are important issues to consider. Palliative RT to localized symptomatic masses produces high response rates even in chemoresistant disease.[178-181]

Patients who experience late relapse (i.e., more than 6 months from the completion of the initial chemo) are referred to as "platinum sensitive," and the probability of having a prolonged progression-free interval is good. The longer the initial treatment-free interval, the higher is the chance of response to second-line chemo, and probability of obtaining a meaningful disease-free interval.[182,183] Second-line chemo is usually retreatment with a platinum-based regimen. The estimated response rate is 30% to 70%.[184-186] Combination second-line chemo versus single-agent platinum has been compared in several studies.[184,185,187] ICON4/AGO-OVAR, a combined analysis of two parallel studies including 804 patients who were platinum-sensitive, compared carboplatin-paclitaxel to "conventional platinum-based chemotherapy" (single-agent carboplatin in the majority).[185] The median OS benefit for the combination was 5 months (29 months versus 24 months). CALYPSO, a randomized Phase III trial comparing pegylated liposomal doxorubicin (PLD) and carboplatin versus paclitaxel and carboplatin in patients who were "platinum-sensitive" with recurrent disease enrolled 976 people.[188] The trial, designed as a noninferiority study found PLD-carboplatin to have a superior PFS (11.3 months versus 9.4 months, HR, 0.821; CI 95%, 0.72 to 0.94) and had a superior toxicity profile including lower rates of severe and long-lasting neuropathy. The final results showed comparable median OS of PLD-carboplatin (30.4 months) and paclitaxel-carboplatin (33 months) (HR, 0.99; 95% CI, 0.85 to 1.16).[188]

Additional studies comparing platinum to platinum and gemcitabine or to platinum and epirubicin have all showed a superior response rate for the combination regimens.[189,190] Thus, the preferred regimen is platinum-based combination chemotherapy with a current recommendation for carboplatin-paclitaxel or PLD-carboplatin.

Molecular-targeting therapies have evolved as an important part of treatment in the recurrent setting. In 2012 the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Diseases (OCEANS) trial assessed the role of bevacizumab in the treatment of platinum-sensitive relapses.[191] This placebo-controlled, Phase III trial of chemotherapy (gemcitabine + carboplatin) with or without bevacizumab enrolled 242 patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Median PFS was 12.4 months versus 8.4 months respectively in the bevacizumab and control arms. (HR progression, 0.484; 95% CI, 0.388 to 0.605). Bevacizumab-associated toxicities including hypertension were noted, but there were no cases of gastrointestinal perforations.

Additional studies are also exploring PARP inhibition specifically in women with *BRCA* mutations. Final results of a GOG Phase II study are pending (GOG 208). Initial results of 48 patients show 7% had a response; 21 were still receiving study drug.[192] Currently, a Phase III trial assessing the role of PARP inhibitors in *BRCA* carriers in the recurrent setting is open to recruitment.

Patients who do not respond to second-line carboplatin-paclitaxel are considered platinum resistant and have a low probability of responding to alternative regimens. Response rates to third-line chemotherapy including liposomal doxorubicin, topotecan, oral etoposide, and gemcitabine are 15% to 25%.[174,176,193,194]

Salvage WAI for ovarian cancer has also been reported. Sedlacek et al[195] evaluated WAI in 27 patients with recurrent ovarian cancer. Their treatment protocol included 30 Gy to 35 Gy, followed by a pelvic boost. OS at 1 and 5 years was 66% and 15%, respectively.

Secondary Cytoreductive Surgery for Disease Relapse

Technically, secondary debulking can be performed in 25% to 85% of patients.[196-198] It is commonly considered most likely to benefit patients with late relapse and resectable tumor, but the likelihood for and benefits of successful secondary debulking are not understood. Its intent is to remove recurrent tumor and thereby prolong the disease-free interval and survival.

Successful secondary debulking is limited. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial is the largest series ($n = 267$ patients) published on the benefit of secondary cytoreductive surgery for recurrent ovarian cancer.[199] Complete resection was associated with significantly longer survival compared with surgery leaving any postoperative residuum (median 45.2 versus 19.7 months; $p < 0.0001$). Variables associated with complete resection were performance status, stage, residual tumor after primary surgery, and absence of ascites of more than 500 mL. An optimal resection was achieved in 79% of patients with all favorable prognostic factors. The EORTC attempted a randomized trial to evaluate the benefit of cytoreductive surgery in recurrent ovarian cancer, but it was closed because of poor accrual. A review of 17 publications of secondary cytoreductive surgery by Hauspy and Covens[200] concluded that patients with favorable characteristic (good performance status, long disease-free interval, and a single or few small intraabdominal sites of relapse) are the ideal candidates that may benefit from secondary cytoreductive surgery.

The most common site of relapse in ovarian cancer is IP with ascites and masses. Bowel complications frequently occur before general deterioration is profound. Comprehensive palliative care is required for all such patients. Partial bowel obstruction is treated conservatively with intestinal decompression and IV hydration. If bowel obstruction is complete or if conservative measures fail, palliative surgery performed to relieve bowel complications may be considered. In patients with an impaired performance status, extensive disease, and limited life expectancy, including multiple levels of obstruction, palliative measures without surgical intervention should be considered.

Intraoperative Irradiation for Locoregional Relapse

In patients with recurrent ovarian cancer localized in the pelvic sidewalls or paraaortic or pelvic lymph nodes, the use of aggressive surgery and intraoperative irradiation (IORT) alone or plus external beam irradiation (EBRT), appears beneficial when compared with "standard" EBRT salvage. Excellent results have been found in IORT series from both Mayo Clinic Rochester[201,202] and Stanford University.[203]

The Mayo Clinic Rochester (MCR) electron beam IORT (IOERT) series of 148 patients with gynecologic cancer included 16 with recurrent ovarian cancer.[201,202] In this highly select group of patients, 2-year OS was 61% and 5-year OS 54%. In an updated MCR analysis,[197] 20 patients with recurrent ovarian cancer received IOERT as a component of treatment and 16 of 20 also received perioperative EBRT (median 50 Gy, range 20 Gy to 54 Gy). With median follow-up of 76 months in surviving patients, 5-year OS was 49%.

Twenty-four patients had maximal resection of recurrent ovarian cancer followed by orthovoltage IORT at Stanford University, and 22 were evaluable for analysis.[203] Most had cytoreductive surgery plus chemotherapy at initial diagnosis; the mean disease-free interval was 48.2 months before resection or IORT. After maximal resection, residual disease was either microscopic (R1) or less than 0.5 cm (R2). The median IORT dose was 12 Gy (range, 9 Gy to 14 Gy). Postoperative EBRT (14 patients) or chemotherapy (6 patients) was given to 20 of 22 patients and was individualized based on sites of relapse and prior therapy (EBRT: abdominal/pelvic, 9; pelvic, 4; inguinal, 1). With median follow-up of 24 months, 5 patients remained free of disease. The 5-year OS was 22%, with a median survival of 26 months from the time of IORT.

Palliative Radiation Therapy

Palliative RT in ovarian cancer is effective in patients with symptoms because of localized disease. It is often a forgotten or ignored modality. In cases of vaginal bleeding, localized pain resulting from masses in the abdomen or retroperitoneum, or disseminated disease (e.g., brain metastases, supraclavicular nodes), RT can induce tumor regression and provide symptomatic relief.[180] Investigators from M. D. Anderson Cancer Center published a 55% response rate for pain palliation and 71% for vaginal bleeding with one to three fractions of 10 Gy.[181] However, 6 of 42 patients developed bowel radiation injury attributed to the large fraction size. A study from Fox Chase Cancer Center[204] reported the use of palliative RT in 33 patients with symptomatic ovarian cancer. Complete palliative response was noted in 51%, and the overall response rate was 79%. Vaginal bleeding and pain were controlled in 90% and 83% of patients, respectively. The median duration of palliation was 4 months, which reflected palliation until death in 90% of cases. In an additional study, from Memorial Sloan Kettering Cancer Center, the median duration of response was 11 months (range, 1 to 86) and closely approximated the survival rate. Additional studies show a similar benefit for palliative RT.[180,181,204,205] Recommendations on the optimal dose for palliation of soft-tissue masses are difficult to make because no comparative trials have been conducted and each center or oncologist uses different doses. No data support the common contention that palliation of symptoms or duration of symptom relief is greater with higher doses of radiation. However, it is obvious from the literature that RT is an effective modality in palliation for ovarian cancer even if the tumor is resistant to multiple lines of chemotherapy.

TREATMENT OF NONEPITHELIAL OVARIAN TUMORS

Ovarian Germ Cell Tumors

GCTs of the ovary are derived from the primordial germ cells of the ovary. They account for less than 5% of all ovarian malignancies and occur predominantly in young patients.[206] In the first two decades of life, GCTs account for two thirds of all ovarian malignancies and are rarely found in women older than the age of 30. The World Health Organization classification of GCTs includes dysgerminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, nongestational choriocarcinoma, immature teratoma, and mixed GCTs. Dysgerminomas are the most common subtype, accounting for 40% to 50% of all GCTs. Immature teratomas and yolk sac tumors each comprise about 20%, and the other subtypes are extremely rare.

GCTs are rapidly growing tumors that frequently present as abdominal pain as a result of capsular distention, torsion, or hemorrhage or to menstrual irregularities. Physical examination and ultrasonography assist in making the diagnosis of an ovarian mass; differentiation between a benign and malignant mass can only be made by histology. Serum markers including β-human chorionic gonadotropin (β-hCG), lactate dehydrogenase (LDH), and α-fetoprotein (AFP) can be useful in helping to identify the presence of a GCT (eTable 61-1). Solid adnexal masses larger than 2 cm in premenarcheal girls or a growing mass with or without elevated tumor markers in menarcheal girls or young women is an indication for exploration. Ovarian GCTs (specifically gonadoblastoma and dysgerminoma) can be associated with dysgenetic gonads. Therefore, in premenarcheal girls with a gonadoblastoma or dysgerminoma, a karyotype should be obtained. Staging of GCTs is per the FIGO staging of epithelial ovarian cancer (see Table 61-1).

Because GCTs predominantly present in young women and are sensitive to postoperative chemo, fertility-sparing surgery is indicated even if the contralateral ovary is involved. The need for a staging procedure is controversial, particularly if adjuvant chemo will be recommended anyway. Many centers do consider careful inspection of the abdomen and pelvis by a trained gynecologic oncologist, with biopsy specimens taken from suspicious areas being adequate. Published recommendations for an appropriate staging procedure for ovarian GCTs[207] include peritoneal washings for cytology, a unilateral salpingo-oophorectomy, and biopsies of the omentum, contralateral ovary, and locoregional lymph nodes.[208] GCTs predominantly spread to retroperitoneal lymph nodes, in contrast to transcoelomic spread of epithelial ovarian cancer. A high proportion of the diagnoses are made after a gynecologist or general surgeon has performed surgery (usually unilateral salpingo-oophorectomy without staging). The value of reoperation is unclear. There is consensus that if observation without adjuvant therapy is adopted there is a need for close surveillance to detect and treat recurrence early. This includes frequent clinic visits and a combination of study of tumor markers and imaging.[208] The exact protocol differs among oncology centers.

Where there is no residual disease, the indication for and use of adjuvant chemo differs among oncology centers. The response to salvage chemo is good and survival rates appear comparable in many cases between those treated with adjuvant therapy versus treatment at the time of relapse. Serum tumor markers can assist in the early detection of recurrence in nondysgerminomas.[209]

Nondysgerminoma

The evolution of chemo for GCTs has been based on the successful treatment of similar histology and, more commonly, testicular GCTs. Initially, patients with advanced ovarian GCTs were treated with surgical debulking, followed by vincristine, dactinomycin, and cyclophosphamide chemotherapy (VAC regimen), with cure rates of approximately 50%.[210,211] As a result of the high cure rates achieved even in advanced testicular GCT using cisplatin, vinblastine, and bleomycin, the GOG evaluated a similar regimen in ovarian GCTs and noted a 70% 4-year OS.[211] Etoposide reduced toxicity and improved cure rates in testicular GCTs. Using three to four cycles of bleomycin, etoposide, and cisplatin (BEP regimen) led to its adoption as the standard regimen for ovarian GCTs, with a 79% to 83% PFS.[212,213] Patients who have no evidence of disease

eTABLE 61-1 Tumor Markers in Malignant Germ Cell Tumors of the Ovary

	AFP	β-hCG	LDH
Dysgerminoma	–	±	+
Immature teratoma	±	–	–
Yolk sac tumor	+	–	–
Choriocarcinoma	–	+	–
Embryonal carcinoma	±	+	–

AFP, *(α-fetoprotein);* β-hCG, *beta-human chorionic gonadotropin;* LDH, *lactate dehydrogenase.*

after surgical staging followed by three cycles of a BEP regimen can expect a 96% to 100% PFS.[208,214]

Most centers treat all tumors except stage IA grade-1 immature teratoma with postoperative chemotherapy. Recently, a large study of observation only for all stage IA GCTs showed a relapse rate of 36% for nondysgerminomatous tumors and 22% for dysgerminomas.[215] Relapse after observation has high salvage rates with the BEP regimen; all but 1 patient who experienced relapse was salvaged. As patients are young, and long-term risks from chemotherapy are relevant, a strong argument can be made for observation.

Disease relapse after primary chemo is treated primarily with second-line agents; infrequently, cure may require ablative regimens and bone marrow transplant. Palliative RT can be used in specific cases after chemo failure.

Dysgerminoma

Dysgerminoma, the most common of germ cell tumors, accounts for approximately 1% of all ovarian cancers. The majority occur between the ages of 10 and 30. Stage IA is the most common stage at diagnosis, representing 75% of all cases.[212] Ten percent may involve both ovaries. It predominantly spreads in an orderly progression to retroperitoneal lymph nodes, in contrast to the transcoelomic spread of epithelial ovarian cancer. LDH is a nonspecific tumor marker and is reported to be elevated in up to 95% of cases[209] β-hCG may be produced in low levels (<200 IU/L).

Young patients found to have stage IA dysgerminoma are usually treated with fertility-sparing surgery without adjuvant chemo or RT. Surveillance for clinical stage IA ovarian dysgerminoma is safe and effective in reducing unnecessary use of chemotherapy, with 10-year OS of 91% in the prechemo era, where relapse was commonly salvaged with RT, to which it is exquisitely sensitive.[216] Relapses usually occur within 2 years of diagnosis, and the relapse rate for stage IA is approximately 20%.[215]

Despite its radiosensitivity, extra-ovarian disease at diagnosis or relapse is usually treated with chemo because of the negative impact of RT on fertility. The BEP regimen and the EP regimen (etoposide/platinum) are the most common combination regimens used because they spare fertility; however, significant side effects do occur.[217,218] As all patients with an ovarian dysgerminoma are young, short- and long-term effects from chemo such as bleomycin-induced lung toxicity and secondary malignancies should be taken into consideration when deciding on treatment.[219-221]

Survival after diagnosis of ovarian dysgerminoma is good even when disseminated disease is found at time of diagnosis. The 5-year OS is higher than 90%.[222,223]

Immature Teratoma

Immature teratomas are composed of tissue that resembles embryonic elements, most commonly nervous system components, bone, cartilage, mucinous fluid, and hair, although any tissue may be seen. Microscopic examination reveals tissue from all three germ layers, with at least some of the components having an immature appearance. The majority of patients do not have an identified serum tumor marker; however, AFP can be elevated in cases with immature gastrointestinal elements.[224]

The treatment recommendation is an initial staging procedure for all patients; however, because most patients are only diagnosed after the final pathologic findings, reports of more limited surgery are common. Treatment decisions are commonly made based on pathology, imaging, and tumor markers.[225-227]

Immature teratomas are graded based on the amount of immature neural tissue they contain, and grade is correlated with prognosis. Norris et al,[228] in 1975, reported the prognosis of 58 patients with a pure immature teratoma treated with surgery: 16 patients were treated with RT or non–platinum-based chemotherapy either after surgery or at time of relapse. Survival of patients with grades 1, 2, and 3 were found to be 81%, 60%, and 30%, respectively. Patients with stage IA, grade-1 tumors can expect an excellent prognosis without the need for adjuvant chemo, and postoperative observation is recommended.

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumors, also called endodermal sinus tumors, are derived from the primitive yolk sac. The majority of tumors secrete AFP, and there is a good correlation between the levels and the extent of disease.[209] Microscopically, Schiller-Duval bodies, a cystic space lined by endothelium with a central vascular area resembling a glomerulus, are characteristic. The median age at diagnosis is 17, with approximately one third of cases diagnosed in premenarcheal girls. Most patients present with stage I disease.[228]

Surgical treatment usually includes unilateral salpingo-oophorectomyas involvement of the contralateral ovary is rare. Although yolk sac tumors present at an early stage, the relapse rate is high. Therefore, some physicians advocate treating all patients with adjuvant chemotherapy.[229] Others believe it is reasonable to observe patients with stage I disease because AFP is elevated in the majority of cases and can be used as a serum tumor marker for early detection of relapse along with imaging. Serial AFP levels are used to monitor response to treatment.

Ovarian Sex Cord and Stromal Tumors

Sex cord and stromal tumors of the ovary account for approximately 5% of all ovarian malignancies. They can occur in patients of all ages, and a significant proportion is diagnosed in patients younger than 40 years old. The cells originate from the sex cords and mesenchyme of the embryonic gonad. Granulosa and Sertoli cells are derived from the sex cord cells; pleuripotential mesenchymal cells are the precursors of Leydig and theca cells, and fibroblasts. The most common type, granulosa cell tumors, constitutes 70% of all sex cord and stromal tumors.

Sex cord and stromal tumors have the ability to produce hormones, especially estrogen or testosterone. They account for 90% of all hormone-producing tumors. The presenting symptoms such as precocious puberty, virilization, or abnormal menstruation in the premenopausal age group or postmenopausal bleeding in the older group are the result of the hormonal elaboration from the tumor itself, or, in the majority of cases, as a result of a nonspecific stromal response in the ovarian tissue. Approximately 60%, of sex cord and stromal tumors, present as stage I.

Granulosa Cell Tumors

Granulosa cell tumors can occur at any age, with a peak in the fifth and sixth decades of life.[230] Two granulosa cell tumors have been separated into the adult type (95%) and juvenile type (5%) based on clinical and histologic characteristics. The main presenting symptoms are abnormal vaginal bleeding, abdominal pain, or distention. Tumors are frequently diagnosed at a large size, more than 10 cm in diameter. Because of the potential estrogen production of granulosa cell tumors, evaluation of the endometrium is important. Endometrial hyperplasia and cancer has been noted in up to 50% and 5% of patients, respectively, at diagnosis.[220] Microscopically, Call-Exner bodies (granulosa cells in rosettes around a central cavity resembling primordial follicles) can be seen. Granulosa

cell tumors spread by transcoelomic, lymphatic, and hematogenous routes, and metastases can develop in parenchymal organs (liver, brain, lungs). Inhibin is a tumor marker that is secreted by some granulosa cell tumors.[231]

The cornerstone of treatment is surgical resection. For women presenting at a young age, fertility-sparing surgery is an option after a negative endometrial biopsy. In a recent retrospective review[232] of 58 patients with sex cord and stromal tumors who underwent lymphadenectomy as part of their initial surgical procedure, none was found to have nodal involvement; thus, lymph node dissection seems unnecessary. Patients with granulosa cell tumors tend to experience relapse years after initial treatment. Because of late relapse, survival declines over decades; there is a significant difference between the 10-year and 20-year OS (90% and 50% to 75%, respectively).[233] In most stage IA cases, surgery alone is curative, although in patients with high-risk factors (large tumor size > 10 cm, tumor rupture, high mitotic index), adjuvant chemo may be considered, although its benefit is unproven.[234,235] Patients with disease spread outside the ovary (stages II to IV) are traditionally treated with postoperative adjuvant chemo, although benefits are unproven. Both chemotherapy and RT produce responses and are used in the recurrent setting.[234]

A Phase II GOG trial evaluated the efficacy of the BEP regimen in completely resected or recurrent sex cord and stromal tumors. Forty-eight of 57 patients had granulosa cell tumors. The response rate for primary disease was 69% (11 of 16), and for recurrent disease it was 51% (21 of 41).[236]

Pankratz et al[237] retrospectively evaluated the prognosis of 61 patients with granulosa cell tumors, 48 of who received postoperative RT. The patients who received postoperative RT had a lower mortality in comparison to those who were not treated with RT even though the stage distribution was in favor of the nonirradiated group. However, the improved OS was not statistically significant and specific data are lacking to make conclusions. Other studies have not shown a benefit of adjuvant RT.[220,234]

Relapses are often isolated intraabdominal or pelvic masses. Accordingly, further surgical resection or localized RT may control disease for protracted periods of years.

IRRADIATION TECHNIQUES

EBRT Technique

When used as a primary or consolidative adjuvant therapy, surgical staging information, as well as analysis of patterns of failure, suggests that to be effective the EBRT volume must include all peritoneal surfaces. Dembo et al[113] emphasized the necessity of covering the diaphragm with adequate margin during all phases of normal respiration.

In general, patients treated with WAI should undergo CT treatment planning in the supine position with arms placed on the chest, or above the head, with appropriate immobilization. Given the importance of treating the entire diaphragm, customized shielding above the diaphragm should allow full irradiation during all cycles of respiration but also attempt to minimize pulmonary and cardiac irradiation. The use of "four-dimensional" CT can allow customized shielding during all phases of quiet respiration. Alternatively, CT at full expiration will have the diaphragm at the most cephalad position, and if shielding is designed at that point in respiration, diaphragmatic coverage can be assured. This technique may result in increased pulmonary and cardiac RT. Coverage of the diaphragm at quiet respiration with four-dimensional CT is preferred.

The inferior edge of the field should be placed below the pelvic floor, generally below the level of the obturator foramen.

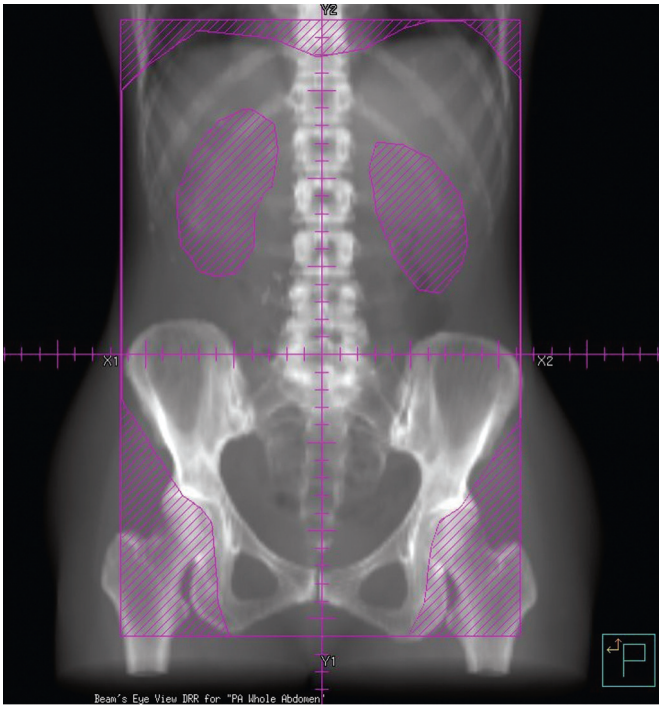


Figure 61-4 A typical whole-abdomen irradiation field.

The lateral edges of the field should be beyond the peritoneal reflection. Current WAI should be performed with an open-field technique, often at an extended source-to-skin distance. Previous use of a moving strip technique has been replaced with an open field technique, given the modern RT machines. The dose to the whole abdomen is generally limited to 22.5 Gy to 30 Gy in 1.0 Gy to 1.5 Gy per fraction. There is no obvious dose response, with a randomized trial noting no benefit to an abdominal dose of 27.5 Gy as compared with 22.5 Gy.[238] That being said, if doses above 25 Gy are used, there should be a consideration for liver shielding to keep the mean liver dose at approximately 25 Gy. In addition, the kidney dose should be limited to approximately 18 Gy. Given the use of the anterior-posterior/posterior-anterior (AP/PA) field, the most common technique is to use the PA shield for most or all of the PA treatments. Further shielding to block the bony pelvis and femoral heads, although delivering the full dose to the entire peritoneum, should be accomplished. Dose-volume histograms (DVH) should be obtained for the liver, kidney, and spinal cord to ensure that these organs are properly shielded. In addition, DVH analysis of the lungs and heart should also be accomplished with dosing to these organs minimized. Figure 61-4 depicts a typical WAI field.

In general, most studies have used a pelvic boost after WAI, for a total pelvic dose of 45 Gy to 50.4 Gy. This should be accomplished with standard pelvic RT techniques rather than IMRT to deliver tumor dose to all peritoneal surfaces. A repeat CT treatment planning session with the patient in a prone position, with a full bladder and possible abdominal compression, should be considered. Paraaortic boost for nodal disease or boost to residual disease should also be considered on an individual basis. If a paraaortic boost is accomplished, the spinal cord dose should be limited to 45 Gy.

Newer WAI treatment techniques have been developed to improve target coverage while reducing radiation to organs at risk, including the bone marrow. This can be particularly important in patients who are receiving chemotherapy and RT. Dosimetric studies have noted improved coverage of the

planning treatment volume and sparing of organs at risk with IMRT.[239] A recent Phase I study noted the feasibility of IMRT WAI as a consolidation after chemotherapy.[240] Helical tomotherapy also has been evaluated with improved dosimetric outcome.[241] All techniques must ensure delivery of tumor dose to the entire peritoneum.

Phosphorus-32

^{32}P is injected into the peritoneal cavity via an intraabdominal port or catheter. This is generally preceded by injection of contrast medium or a technetium-labeled radionuclide, followed by imaging to ensure adequate flow throughout the abdomen, including the cul-de-sacs and infradiaphragmatic region. After adequate flow has been determined, radioactive chromic phosphate ^{32}P (10 mCi to 20 mCi) is injected into the peritoneal cavity along with saline. Patients are then asked to move positions frequently to ensure good distribution through the peritoneal cavity.

TREATMENT ALGORITHMS, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

The treatment of epithelial ovarian cancer is guided by the extent of disease at the time of diagnosis. Patients with disease confined to the ovary undergo a staging procedure to assess extent of microscopic dissemination that necessitates adjuvant chemotherapy. Certain early-stage histologies may benefit from adjuvant RT (clear cell, endometrioid, mucinous). Patients diagnosed with advanced disease undergo either a primary debulking procedure (to remove the maximum amount of macroscopic disease) or neoadjuvant chemo and interval debulking. The treatment algorithm presented in Figure 61-5 represents the current standard of care.

Challenges and Future Possibilities

Epithelial ovarian cancer remains a challenging cancer to treat as the majority of patients are diagnosed with advanced disease; although the response to chemo is high, most patients will eventually succumb to their disease. In the past decade, a modest improvement in survival has been demonstrated with the introduction of intraperitoneal chemotherapy. The specific timing and extent of debulking surgery together with the optimal chemo regimen are still controversial and will remain so until future results of current studies become available and the outcome becomes clearer. As technology improves, consolidative RT may play a role as the toxicity ratio is improved.

The role of RT for both early-stage and locoregional relapse needs to be clarified. Certain early-stage histologies (clear cell, endometrioid, and mucinous carcinomas) may benefit from adjuvant RT, as discussed previously, and this potential indication continues to evolve. The role of irradiation (EBRT, IORT,

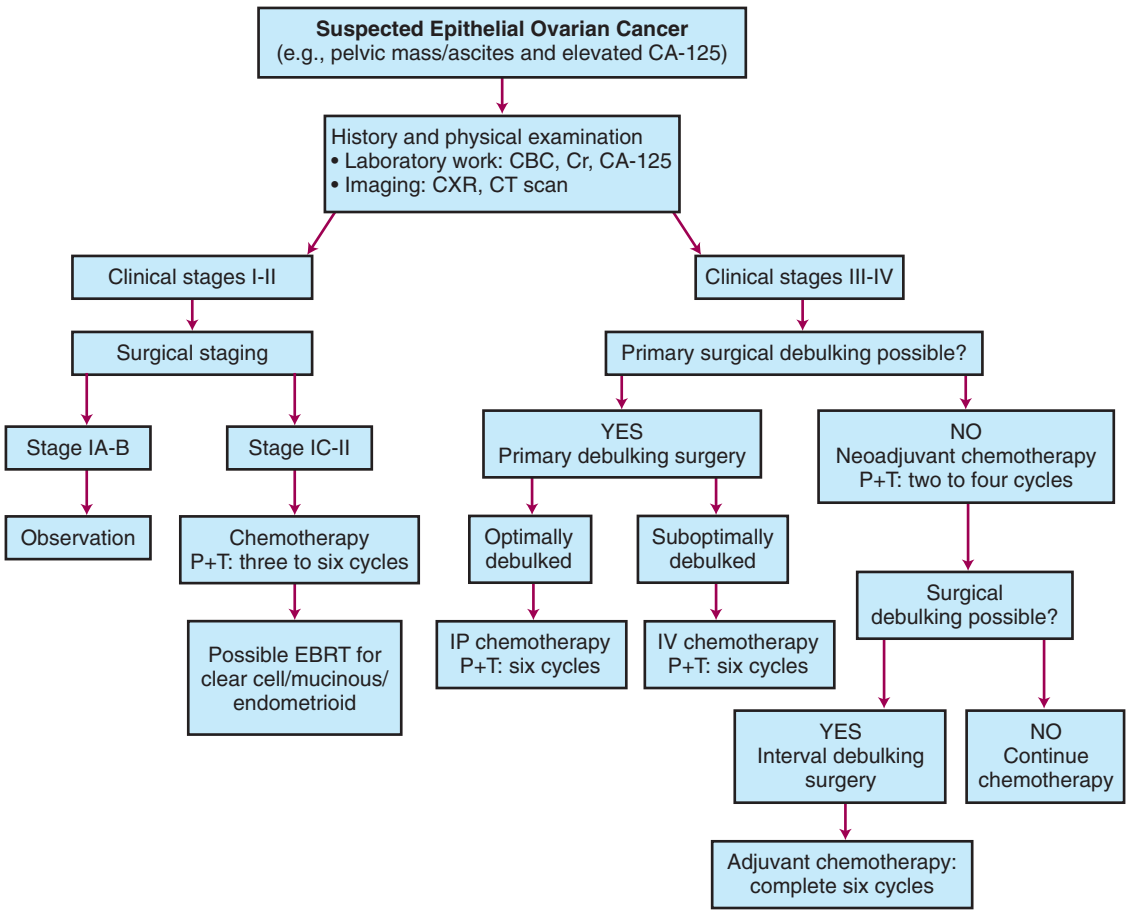


Figure 61-5 Treatment algorithm for epithelial ovarian cancer. *AFP,* α-fetoprotein; *β-hCG,* beta-human chorionic gonadotropin; *CBC,* complete blood count; *Cr,* complete response; *CT*, computed tomograph; *CXR,* chest x-ray; *EBRT,* external beam radiation therapy; *IP,* intraperitoneal; *IV,* intravenous; *P+T,* platinum plus taxane chemotherapy.

and even SBRT for localized masses) as a component of aggressive salvage treatment for select patients with locoregional relapse also needs to continue to be evaluated.

Multiple novel therapies, including PARP inhibitors and antiangiogenic drugs, have also shown promising results. The further understanding of the pathogenesis of ovarian cancer will potentially lead to the exploration and development of additional novel therapies based on the molecular signature of the tumor.

For specific patients who harbor a predisposition to the development of epithelial ovarian cancer, prophylactic surgery has been shown to prevent its development and should be recommended. Early detection has not yet been shown to be effective in high- or low-risk populations and should not be relied on at this time.

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A full list of cite reference is published online at www.expertconsult.com.

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