Part II Disease Sites

12

High-Grade Serous Carcinomas of the Ovary, Fallopian Tube, and Peritoneum

David E. Cohn, Ronald D. Alvarez

INTRODUCTION

Epithelial ovarian, fallopian tube, and primary peritoneal cancers remain the most lethal of all the gynecologic malignancies. In 2010, approximately 21,880 women will be diagnosed with ovarian cancer in the United States; of these, 13,850 will be expected to die from this disease[1]. Cancers arising from the fallopian tube and peritoneum are significantly less common that those arising from the ovarian epithelium, but share several similarities in their epidemiology, diagnosis, treatment, and associated outcomes. As the vast majority of fallopian tube and primary peritoneal cancers exhibit a high-grade papillary serous histology, comparisons to similar disease in primary ovarian cancers suggest common molecular pathways that may promote carcinogenesis within the serous classification of these tumors. Several recent hypotheses also propose a fallopian tube origin for metastatic disease that would traditionally be considered as primary ovarian or peritoneal. Given the recent advances surrounding these diseases, this chapter will consider this subset of high grade serous reproductive cancers as a group, with specific differences highlighted.

EPIDEMIOLOGY

Key Points

1. Women with an inherited ovarian cancer syndrome, particularly those with mutations in the BRCA 1 and 2 genes, have the highest lifetime risk of developing high-grade, papillary serous epithelial ovarian, primary peritoneal, and fallopian tube cancer.
2. For ovarian cancer, epidemiologic factors that are associated with an increase in lifetime ovulatory cycles confer an increased risk.
3. Bilateral salpingo-oophorectomy, oral contraceptives, tubal ligation, and hysterectomy are all well established risk modifiers of epithelial ovarian, fallopian tube, and primary peritoneal cancer.

Epidemiologic data indicate that ovarian cancer is the 9th most common malignancy affecting women in the United States, with 21,880 cases predicted for 2010; unfortunately, it is the 5th most common cause of cancer-related deaths, with 13,850 women estimated to die of this disease in the same time period.1 The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with a rate of 57 per 100,000 women. The median age at diagnosis is 63 years, and 70% of patients will present.

The true incidence of fallopian tube and primary peritoneal malignancies is more difficult to quantify. Despite criteria established by the Gynecologic Oncology Group to define primary peritoneal cancers, uniform application by pathologists remains unclear, which clouds identification of the true incidence of this disease. High-grade serous carcinomas of the fallopian tube are rare entities, with 3,479 new cases expected to be diagnosed yearly[3]. However, incomplete pathologic sectioning and evaluation of the tubes in women with presumed metastatic ovarian cancer may preclude identification of a true tubal origin. Recent

evidence suggests nearly 60% of all high-grade, non-uterine serous cancers initially classified as primary ovarian or peritoneal in origin demonstrate serous tubal intraepithelial carcinoma (STIC), suggesting that the fallopian tube may be the organ of origin.[4, 5]

One of the strongest risk factors for the development of serous gynecologic cancers is the presence of a genetic predisposition to the disease. The majority of patients with a genetic predisposition to ovarian cancer have mutations in the BRCA1 or BRCA2 genes. As such, a personal or family history of premenopausal breast cancer or any ovarian cancer suggests that the presence of a BRCA gene mutation is more probable, and thus increases the risk of these diseases *(Table 12-1)*.

Epithelial ovarian cancer is, however, a disease that occurs most commonly as a result of sporadic (non-inherited) acquisition. The median age of patients diagnosed with epithelial ovarian cancer is in the early 7th decade. Epidemiologic studies have established several specific risk modifiers that are associated with an increased risk for the development of ovarian cancer, including increased lifetime exposure to ovulation. These factors include a longer duration of menstruation (early menarche, late menopause), nulliparity, and lack of breast feeding6. While it would intuitively make sense that medications that induce ovulations (such as those used for the treatment of infertility) would increase the risk for ovarian cancer, this has only been suggested but not proven. Ovarian cancer occurs more frequently in industrialized countries, where obesity and a high-fat diet are more common. The hormonal basis of ovarian cancer is less certain, with some studies associating menopausal estrogen replacement with an increased risk, and others with a decreased or no impact on the disease[7].

Table 12-1 Risk Factors for Ovarian Cancer

Increased risk
Advancing age
Residence in developed world
Nulliparity
No breast feeding
Early menarche
Late menopause
Obesity
Menopausal estrogen replacement (variable association)
Perineal talc exposure (variable association)
Infertility medications (variable association)
Personal or family history of premenopausal breast cancer or any ovarian cancer
Decreased risk
Oral contraceptives
Hysterectomy
Tubal ligation
Oophorectomy

Protection against ovarian cancer may be provided through several interventions. Factors that decrease ovulation, such as oral contraceptives, decrease the risk of the disease both in patients with and without a genetic predisposition to developing ovarian cancer. Removal of the ovaries will in large part guarantee the prevention of ovarian cancer, though rare cases of adenocarcinoma of the peritoneal cavity (primary peritoneal cancer) can occur in high-risk women. Likely due to the disruption of the ovarian blood supply, hysterectomy also decreases the risk for developing ovarian cancer. Given the relationship between peritoneal and iatrogenic irritants (possibly such as talc) and ovarian cancer, tubal ligation has been proven to decrease the risk of the disease as well.

High-grade papillary serous epithelial malignancies can arise from numerous anatomic locations in the gynecologic system, including the ovaries, peritoneum, uterus, and cervix. This chapter will focus on the most common sites of epithelial serous malignancies: the ovaries, fallopian tubes, and peritoneum. Epithelial ovarian and peritoneal cancers are predominantly of serous histology (85%), and histologically recapitulate the appearance of the fallopian tubal epithelium. The remaining histologies of epithelial ovarian cancers (endometrioid, mucinous, clear cell and Brenner tumor) are discussed in Chapter 13.

Serous adenocarcinomas of the ovary, peritoneum or fallopian tubes can be cytologically low-grade or high-grade, with high-grade adenocarcinomas comprising over 80% of all serous cancers. The clinical importance of segregating invasive ovarian neoplasms by cytology relates to the strong influence of grade on the biologic behavior of these. Comparisons of low-grade to high-grade serous ovarian cancers shows differences in genetics, response to chemotherapy and survival. The "two-tier" system has been shown to be both reproducible and biologically relevant. High-grade serous cancers are generally diagnosed at advanced stages, and are responsive to taxane and platinum chemotherapy. Low-grade serous cancers are considered to be chemotherapy resistant, and may not respond as robustly to the adjuvant chemotherapy generally administered to patients with ovarian cancer8. In fact, genetic profiling of low-grade serous cancers demonstrates distinct fingerprints from high-grade tumors, with segregation closer to the profile of borderline cancers.[9] These studies have been invaluable in providing insight into potential molecular targets for the treatment of low-grade serous cancers.

Recently, increasing attention has been paid to the biology and pathogenesis of ovarian cancer. Whereas historically, high-grade serous ovarian cancer was thought to develop from precursor lesions of the ovarian surface epithelium (mesothelium), with metaplastic changes leading to transformation into malignancy, increasing scrutiny has challenged this long-held theory. It is now hypothesized that the majority of epithelial ovarian and primary peritoneal cancers arise from the fallopian tubes, either from high-grade intraepithelial neoplasia of the tubal epithelium or from the ciliated columnar epithelium residing in the para-tubal and para-ovarian tissues10. While this recent shift in the description of the origin of ovarian cancer is conceptually attractive, it is by no means definitive, and substantial research will need to be completed prior to its universal adoption.

Screening for Ovarian Cancer

Ovarian cancer is a rare disease, with a woman's lifetime risk of being diagnosed approaching 1 in 75 (1.5%) in the general population. The prevalence of the disease is approximately 1 in 2,500 in postmenopausal women. This rate, in contrast with a woman's lifetime risk of being diagnosed with breast cancer (1 in 9, or 11%), is responsible for the challenges of ovarian cancer screening in the general population. In women with an increased risk of developing ovarian cancer as a result of a hereditary predisposition, screening becomes more feasible, as the tests required to detect the disease do not require as high a sensitivity and specificity as with detection of a more rare disease. Given that over 90% of women diagnosed with ovarian cancer have sporadic disease, accurate screening remains a challenge. As such, less than 30% of patients with ovarian cancer are diagnosed with stage I disease (when the 5-year survival rates can exceed 90%).

Currently utilized modalities attempting to identify early stage ovarian cancer (and thus improve survival) have mainly focused on transvaginal pelvic ultrasonography and serum CA-125 testing. While novel serum markers and other imaging technologies are in evaluation, previous and current clinical protocols evaluating the role of ovarian cancer screening have tested pelvic ultrasound and CA-125. To date, there has been no evidence in the general population that routine screening for ovarian cancer reduces mortality related to this disease.[11] However, two ongoing clinical trials are continuing to gather information to assess the value of screening in the general population. The PLCO (prostate, lung, colorectal, ovary) screening trial randomized more than 34,000 postmenopausal women without oophorectomy to both annual CA-125 and pelvic ultrasounds for four years versus routine care. The most recent results from the screening arm demonstrated that 60 of 89 invasive ovarian or peritoneal cancers were detected by screening, although 72% of the screen-detected cases were diagnosed with at an advanced stage.[12] The primary objective of the study, the impact of screening on mortality, has yet to be reported.

In the United Kingdom (UK), the UKCTOCS (collaborative trial of ovarian cancer screening) randomized more than 100,000 postmenopausal women to routine care, versus more than 50,000 postmenopausal women to screening with both pelvic ultrasound and CA-125 versus more than 50,000 to pelvic ultrasound alone. While the data regarding ovarian cancer mortality is not yet mature, preliminary results suggest that the use of multimodality screening with CA-125 and ultrasound is superior to ultrasound alone or routine care in the detection of ovarian cancer13. Recently, a single arm multi-institutional study describing the use of the "risk of ovarian cancer algorithm" (ROCA) interpretation of the trend of multiple CA-125 levels followed by ultrasound for a positive ROCA screen in a general population cohort of 3,251 postmenopausal women over 9 years demonstrated that of the five women diagnosed with ovarian cancer, 3 (60%) had early stage disease, and most had a normal (but increasing by ROCA) level of CA-125 that would have gone without detection by standard CA-125 screening. The ROCA triage strategy was associated with a positive predictive value of 37% and a specificity of 99.9%[14]. Together, these trials suggest that screening of ovarian cancer may be feasible, but data regarding its impact on mortality are imperative for the widespread introduction of this technique into the general population.

DIAGNOSIS

Key Points

1. Women with ovarian cancer often experience symptoms of bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, urinary symptoms (urgency or frequency).
2. The evaluation of a patient with such symptoms or suspected ovarian cancer should include a thorough abdominal pelvic examination, selective imaging studies, and selective tumor markers.

Until recently, many providers have described ovarian, fallopian tube, and peritoneal cancers as a "silent" disease, with the thought that there are no classic symptoms until metastases have developed. There is evidence now to suggest that most women with these cancers, including those with early stage disease, often experience distinct clinical features and

symptoms for several months prior to their initial diagnosis. A national survey of 1500 women, prior to their diagnosis of ovarian cancer, identified common signs that included abdominal, gastrointestinal, pain, constitutional, urinary or pelvic symptoms in nature15. In a landmark prospective case-control study, Goff et al identified four symptoms more likely to occur in women with ovarian cancer than in the general population of women presenting to primary clinics16. These symptoms included an increase in abdominal size, bloating, urinary urgency, and pain. Symptoms in women with malignant ovarian masses were likely to be more recent in onset, more frequent and higher in severity than those experienced by women without an ovarian malignancy. The results of this study and others led to the development of an Ovarian Cancer Symptoms Consensus Statement *(Table 12-2)*[17].

Fallopian tube cancer may present with similar symptoms. A specific clinical entity, "hydrops tubae profluens," is also considered classic for this disease, but is typically not identified in women diagnosed with tubal cancer. This cluster of symptoms includes cramping lower abdominal pain, which resolves after passage of a profuse, watery and/or yellow vaginal discharge.

The importance of both the patient and the clinician recognizing the symptoms suggestive of epithelial ovarian, fallopian tube, or primary peritoneal cancer cannot be understated. Studies have demonstrated that even 80-90% of patients with early stage disease are symptomatic15. Given the lack of effective screening strategies, early recognition of symptoms associated with ovarian cancer may facilitate diagnosis of ovarian cancer at an earlier stage where outcome is improved. Several efforts are underway to develop algorithms that direct the evaluation and management of women who present with symptoms of ovarian cancer that include physical examination by a gynecologist and appropriate imaging and laboratory assessment.

Patients with symptoms such as those previously described should undergo a thorough physical assessment, which should include an abdominal and pelvic examination. Physical examination findings are often based upon the stage of disease. Patients with early stage disease may be found to have an adnexal mass appreciated on abdominal or pelvic examination18.

Table 12-2 Symptoms Likely to Occur More Commonly in Women with Ovarian Cancer than in General Population

Bloating
Pelvic or abdominal pain
Difficulty eating or feeling full quickly
Urinary symptoms (urgency or frequency)

Patients with a malignant ovarian neoplasm may have a mass of various dimensions but typically such masses are solid, irregular, or fixed. However, pelvic examination has limited sensitivity in the detection of adnexal masses; thus, many patients with early or late stage ovarian cancer have a normal pelvic examination19. The adnexal mass may be tender to the patient on palpation but rarely do patients have significant guarding or rebound tenderness. Patients with more advanced stage disease are often found to have, along with a pelvic mass, abdominal distension or a fluid wave indicating the presence of ascites. These patients are often noted to have an upper abdominal mass suggestive of omental metastasis.

Physical examination should also include evaluation of the supraclavicular and inguinal lymph nodes to assess for nodal metastasis and evaluation of the breasts and rectum to assess for cancers originating in these organs. Other aspects of the physical examination should focus on evaluation of the other major organ systems to appropriately assess for co-morbidities that may affect management decisions.

Various imaging studies can be selectively utilized to further evaluate a patient with a pelvic mass or with symptoms suggestive of ovarian cancer[20, 21]. Pelvic and/or transvaginal ultrasound remains the modality of choice to evaluate a patient with an adnexal mass, due to its ease of use and relatively less expense. Pelvic ultrasound can most often distinguish uterine from ovarian pathology and certain features noted on sonography can raise or lower suspicion for malignant disease. Findings most suggestive of malignancy in the postmenopausal woman with an ovarian mass include the presence of excresences or papillary structures within a cyst; size greater than 10 cm; a solid or mixed solid and cystic mass; thickened septa; and color or Doppler demonstration of blood flow in the mass[20, 21]. Recent studies have confirmed the ability of such ultrasound findings alone and in combination with selective tumor markers (CA-125) to be predictive in discriminating between benign and malignant adnexal masses[22, 23].

Abdominal/pelvic CT is also a very useful imaging modality particularly in those patients with nonspecific symptoms suggestive of a malignant ovarian neoplasm or clinical evidence of potential metastatic disease[20, 21]. While not as accurate as ultrasound in characterizing the components of an ovarian mass, abdominal/pelvic CT is able to accurately determine the presence of ascites or metastases to the omentum, peritoneal surfaces, retroperitoneal lymph nodes, or intraparenchymal organs such as the liver and spleen. In addition, valuable information can be ascertained regarding other intraperitoneal organ sites that may be contributing to clinical symptoms and findings or that may be secondarily involved with a malignant ovarian process.

MRI or PET imaging rarely adds to the assessment of a patient with a pelvic mass or evidence of metastases over that which can be achieved with pelvic ultrasound or abdominal/pelvic CT20, 21. MRI may be useful in the setting where there is a sonographically indeterminate or complex pelvic mass and there is uncertainty about the ovary as an origin of the mass. FDG-PET alone or combined with CT have improved sensitivity over CT in the evaluation of an adnexal mass; however, low specificity and false positive physiologic signals are not infrequently noted and rarely does FDG-PET imaging enhance the ability of a clinician to make a management decision over what can be decided with ultrasound or CT imaging.

Serum CA125 may also be very useful in guiding clinical management decisions in patients with symptoms or physical examination findings suggestive of an ovarian neoplasm, particularly in the postmenopausal woman[24, 25]. An elevated CA125 in the presence of an adnexal mass in a postmenopausal woman is highly predictive of a malignant ovarian neoplasm. Care must be exercised in interpreting a normal serum CA125 level in a patient with an ovarian mass as an indication that the patient may not harbor a malignant ovarian mass. Serum CA125 may not be elevated in patients with non-serous (such as mucinous) ovarian neoplasms and is only elevated in approximately 50% of patients with early stage ovarian cancer. OVA1 is a recently FDA approved laboratory test that has assesses five serum biomarkers including CA125, prealbumin, transferrin, beta 2 microglobulin, and apolipoprotein A1[26, 27]. OVA1 is reported to improve the ability of physicians to predict whether an ovarian mass is malignant when used in combination with clinical and radiographic imaging compared to when physicians utilize clinical and radiographic imaging alone. Continued investigation of this multiplex test, as well as others, is needed prior to its establishment as a routine investigation in women with ovarian cancer or as a screening tool[28].

The American Congress of Obstetricians/Gynecologists and the Society of Gynecologic Oncologists have issued guidelines applicable to all primary care physicians that provide recommendations to obstetrician/gynecologists for the evaluation and management of patients with a pelvic or ovarian mass29, 30. The differential diagnosis in a patient with a pelvic mass should take into consideration problems that can arise from all organ systems located within the pelvis. *(Table 12-3)*.

The primary care physician must first have a high index of suspicion for a malignant ovarian neoplasm in patients who present with any of the previously described symptoms or signs commonly experienced in patients with a malignant ovarian mass. A thorough history and physical examination, including an abdominal and pelvic examination, are paramount. Primary care physicians should obtain selective imaging and laboratory studies to evaluate for a possible ovarian neoplasm in women with symptoms or physical examination findings suggestive of an ovarian neoplasm. A pelvic ultrasound can provide useful information about an adnexal mass that can guide clinical management decisions. An abdominal/pelvic CT may be helpful in evaluating whether symptoms may be attributable to other organ systems or, if an adnexal mass is present, whether metastasis are present. A serum CA125 is most useful in determining whether an adnexal mass may be malignant, particularly in the postmenopausal patient. An OVA1 study may also be useful in situations in which a serum CA125 is normal, characteristics of an adnexal mass are not definitive, and concern persists for the possibility of an ovarian malignancy. It is important that primary care physicians take into consideration all clinical, radiographic and laboratory findings to guide management decisions, in particular those findings that may determine the need for surgical evaluation or subspecialty referral.

Table 12-3 Differential Diagnosis of Pelvic Mass

Ovarian
Functional cyst
Benign neoplasm (cystadenoma, cystadenofibroma)
Malignant neoplasm (invasive and borderline cancer)
Fallopian tube
Hydrosalpinx
Tubo-ovarian abscess
Malignant neoplasm
Uterine
Congenital anomaly
Leiomyoma
Other
Colon (diverticular abscess, colon cancer)
Urologic (Bladder obstruction, bladder cancer, pelvic kidney)
Lymphoma
Soft tissue benign or malignant mass

PATHOLOGY

Key Points

1. Metastatic ovarian and primary peritoneal cancer may arise from an abnormal focus in the fallopian tube epithelium.

2. The majority of malignant epithelial ovarian, primary peritoneal, and fallopian tube neoplasms are serous cancers.
3. Staging of gynecologic cancers reflects the distribution of disease, but does not take into consideration other important prognostic factors, such as the volume of disease remaining after surgical resection.

High-grade papillary serous cancers of the ovarian, fallopian tube, and peritoneum share similar histologic characteristics that frequently do not permit determination of the organ of origin. These malignancies are characterized by clusters of atypical cells arranged in papillary patterns with irregular underlying stroma, or may appear as sheets of malignant cells with marked atypia without underlying stroma *[Figure 12-1]*. As with all grade 3 malignancies, the nuclear to cytoplasmic ratio is high, and observation of atypical mitoses is common. Psamomma bodies are more common in low-grade serous malignancies; they are rarely seen in grade 3 disease.

Spread of serous ovarian, tubal, and peritoneal cancer can be through a number of mechanisms, including direct tumor dissemination into the peritoneal cavity, lymphatic spread, and hematogenous spread (into

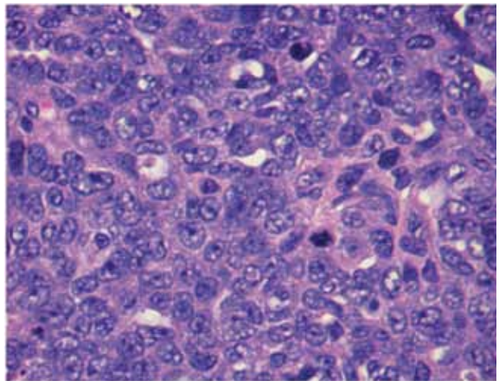

FIGURE 12-1. Photomicrograph of histologic specimen of grade 3 serous adenocarcinoma.

solid organs and bone). The vast majority of patients with advanced serous cancers have peritoneal metastases. For epitihelial ovarian cancer, disease most commonly spreads to the surface of the peritoneal cavity, the serosa of the large or small intestines, the omentum, and the surface of the liver or diaphragm *[Figure 12-2]*. While peritoneal spread of advanced ovarian

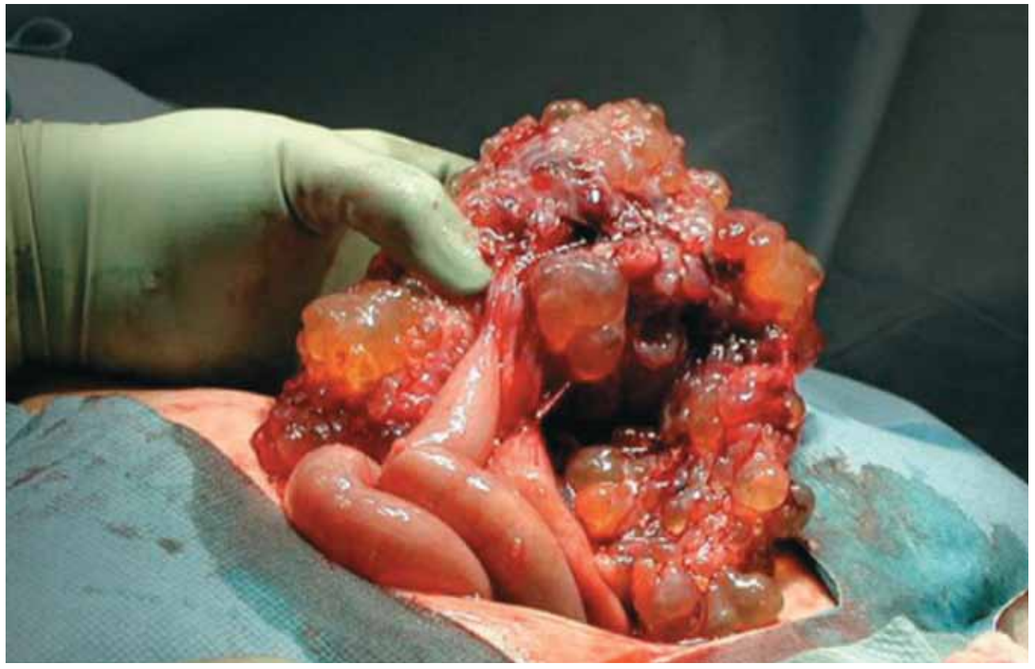

FIGURE 12-2. Photograph showing omental caking caused by tumor invasion.

cancer is quite common, it is estimated that at least 50% of these patients have concurrent or isolated retroperitoneal (pelvic, aortic, celiac) lymph node metastasis31. The rate of solid organ involvement in newly diagnosed ovarian cancer is quite low32, though involvement of solid organs in the context of recurrent disease has been increasing as patients are experiencing increased disease-free survival in the primary and recurrent settings, thus allowing for the manifestations of solid organ metastasis prior to death from peritoneal spread of ovarian cancer. The pattern of spread of peritoneal cancers is similar to that of ovarian cancers, with common dissemination throughout the peritoneal cavity and spread to the peritoneal surface of the pelvis, intestines, diaphragm and omentum. While generally the behavior of these malignancies is similar to those of the ovary and peritoneal cavity, fallopian tube cancers are different in that the rate of disease metastasis to the retroperitoneal lymph nodes exceeds that of the other high-grade serous gynecologic cancers; specifically, in tumors clinically confined to the fallopian tube, over a third have pathologic involvement of the retroperitoneal lymph nodes.[33]

The staging system for ovarian cancer was established to provide a common language for the communication of results regarding diagnosis and treatment of the disease. The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system is shown in *Table 12-4*. While stage clearly is an important prognostic factor in patients with ovarian cancer overall, what is not conveyed in the FIGO staging system is the description of the volume of residual disease following primary cytoreduction in women with advanced ovarian cancer, which has been shown to be the most important prognostic factor in women with metastatic disease. It is important to consider that while distant metastasis (to the upper abdomen or lymph nodes) is generally associated with stage IV disease in most other solid tumors, it is considered stage III in ovarian cancer, with stage IV cases reserved for those with parenchymal liver involvement, cytologically positive pleural effusions, or other extra-abdominal metastasis.

Although the treatment of fallopian tube cancer is identical to that of ovarian cancer, fallopian tube cancers are staged by a separate system. In order for an adnexal malignancy to be designated a high-grade serous fallopian tube (and not ovarian) cancer, specific pathologic criteria must be met. Specifically, all or most of the adnexal malignancy must arise in the fallopian tube, and a transition from benign to invasive neoplasm must be identified in the fallopian tube34, 35. In the absence of these criteria, and adnexal malignancy is classified as an ovarian cancer.

Primary peritoneal cancers are staged similarly to epithelial ovarian malignancies. The Gynecologic Oncology Group established pathologic definitions of primary peritoneal cancer in 1993: (1) The ovaries are normal in size or enlarged by a benign process; (2) The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary; (3) Microscopically, the ovaries are not involved with the tumor or exhibited only serosal or cortical implants less than 5 mm×5 mm; (4) The histopathological and cytological characteristics of the tumor are predominantly of the serous type.[36]

Table 12-4 FIGO Staging of Ovarian (and Peritoneal) Cancer

IA - involves one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IB - involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings
IC - tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings
Stage II - pelvic extension or implants
IIA - extension or implants onto uterus or fallopian tube; negative washings
IIB - extension or implants onto other pelvic structures; negative washings
IIC - pelvic extension or implants with positive peritoneal washings
Stage III - microscopic peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum
IIIA - microscopic peritoneal metastases beyond pelvis
IIIB - macroscopic peritoneal metastases beyond pelvis less than 2 cm in size
IIIC - peritoneal metastases beyond pelvis > 2 cm or lymph node metastases
Stage IV - distant metastases to the liver or outside the peritoneal cavity
Colon (diverticular abscess, colon cancer)
Urologic (Bladder obstruction, bladder cancer, pelvic kidney)
Lymphoma
Soft tissue benign or malignant mass

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
2. Morgan RJ Jr, Alvarez RD, Armstrong DK, et al. Epithelial ovarian cancer. J Natl Compr Canc Netw. 2011 Jan;9(1):82-113.

3. Goodman MT, Shvetsov YB. Incidence of ovarian, peritoneal, and fallopian tube carcinomas in the United States, 1995-2004. Cancer Epidemiol Biomarkers Prev 2009;18:132-9.
4. Seidman JD, Zhao P, Yemelyanova A. "Primary periotneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma. Gynecol Oncol 2010; epub ahead of print.
5. Przybycin CG, Kurman RJ, Ronnett BM, Shih leM, Vang R. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol 2010; 34 (10): 1407-16.
6. Schorge JO, Modesitt SC, Coleman RL, et al. SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol 2010;119:7-17.
7. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab 2010;95:s1-s66.
8. Gershenson DM, Sun CC, Bodurka D, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol 2009;114:48-52.
9. Bonome T, Lee JY, Park DC, et al. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. Cancer Res 2005;65:10602-12.
10. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010 Mar;34(3):433-43.
11. Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. N Engl J Med 2009;361:170-7.
12. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol 2009;113:775-82.
13. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327-40.
14. Lu KH, Skates S, Bevers TB, et al. A prospective U.S. ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA). J Clin Oncol 2010;28:15s (suppl; abstr 5003).
15. Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis – Results of a national ovarian cancer survey. Cancer 2000;89:2068-75.
16. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA 2004;291:2705-12.
17. Ovarian Cancer Symptoms Statement http://www.wcn.org/articles/types_of_cancer/ovarian/symptoms/concensus_statement.html
18. Ettabbakh GH, Yadav PR, Morgan A. Clinical picture of women with early stage ovarian cancer. Gynecol Oncol 1999:75(3):476-9.
19. Padilla LA, Radosevich DM, Milad MP. Accuracy of the pelvic examination in detecting adnexal masses. Obstet Gynecol 2000;96:593-8.
20. Shaaban A, Rezvani M. Ovarian cancer: Detection and radiologic staging. Clin Obstet Gynecol 2009;52:73-93.
21. Iyer VR, Lee SI. MRI, CT, and PET/CT for ovarian cancer detection and adnexal lesion characterization. AJR Am J Roentgenol 2010;194(2):311-21.
22. Van Calster B, Timmerman D, Bourne T, et al. Discrimination between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA-125.
23. McDonald JM, Doran S, DeSimone CP, et al. Predicting risk of malignancy in adnexal masses. Obstet Gynecol 2010;115(4):687-94.
24. Bast RC, Badgwell D. Lu Z, et al. New tumor markers: CA125 and beyond. Int J Gynecol Cancer 2005:15:274-81.
25. Duffy MJ, Bonfer JM, Kulpa J, et al. CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. Int J Gynecol Cancer 2005;15(5):679-91.
26. Feng ET. A recipe for proteomics diagnostic test development: the OVA1 test, from biomarker discovery to FDA clearance. Clin Chem 2010;56(2):327-9.
27. Ueland F, DeSimone C, Seamon L, et al. The OVA1 test improves the preoperative assessment of ovarian tumors . Gynecol Oncol 2010;116:3s (suppl; abstr 54).
28. Muller CY. Doctor, should I get this new ovarian cancer test-OVA1? Obstet Gynecol 2010:116:246-7.
29. American College of Obstetricians and Gynecologists ACOG Committee Opinion: number 280, 2002. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. Obstet Gynecol. 2002;100(6):1413-6.
30. Le T, Glede C, Salem S, et al. Initial evaluation and referral guidelines for management of pelvic/ovarian masses. J Obstet Gynaecol Can. 2009;31(7); 668-80.
31. Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: A randomized clinical trial. J Natl Cancer Inst 2005;97:560-6.
32. Aletti GD, Podratz KC, Cliby WA, Gostout BS. Stage IV ovarian cancer: disease site-specific rationale for postoperative treatment. Gynecol Oncol 2009;112:22-7.
33. Di Re E, Grosso G, Raspagliesi F, Baiocchi G. Fallopian tube cancer:Incidence and role of lymphatic spread. Gynecol Oncol 1996;62:199-202.
34. Hu CY, Taymor ML, Hertig AT. Primary carcinoma of the fallopian tube. Am J Obstet Gynecol 1950;59:58-67.
35. Sedlis A. Carcinoma of the fallopian tube. Surg Clin North Am 1978;58:121-9.
36. Bloss JD, Liao SY, Buller RE, et al. Extraovarian peritoneal serous papillary carcinoma: a case-control retrospective comparison to papillary adenocarcinoma of the ovary. Gynecol Oncol. 1993 Sep;50(3):347-51.
37. Young RC, Decker DG, Wharton JT, et al. Staging laparotomy in early ovarian cancer. JAMA 1983;250(22):3072-6.
38. Le T, Adolph A, Krepart GV, et al. The benefits of comprehensive surgical staging in the management of early-stage epithelial ovarian carcinoma. Gynecol Oncol. 2002;85(2):351-5.
39. Trimble EL. Prospects for improving staging of ovarian cancers. Lancet 2001;357(9251):159-60.
40. NCCN Ovarian Cancer Guidelines. http://www.nccn.org/professionals/physician_gls/ PDF/ovarian.pdf
41. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. Am J Obstet Gynecol. 2005 May;192(5):1614-9.
42. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. N Engl J Med. 1990;322(15):1021-7.
43. Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst. 2003;95(2):105-12.
44. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst. 2003;95(2):113-25.
45. Colombo N, Guthrie D, Chiari S, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. J Natl Cancer Inst. 2003;95(2):125-32.

46. Young RC, Brady MF, Nieberg RK, et al. Adjuvant treatment for early ovarian cancer: A randomized phase III trial of intraperitoneal 32P of intravenous cyclophosphamide and cisplatin – A Gynecologic Oncology Group study. J Clin Oncol 2003;21:4350-5.
47. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2006;102(3):432-9.
48. Mannel R, Brady M, Kohn E, et al. GOG175: A randomized phase III trial of IV carboplatin (AUC 6) and paclitaxel 175 mg/m2 q 21 days x 3 plus low-dose paclitaxel 40 mg/m2/wk versus IV carboplatin (AUC 6) and paclitaxel 175 mg/m2 q 21 days x 3 plus observation in patients with early-stage ovarian cancer. Gynecol Oncol 2010;116:S2. (Abstract)
49. Chan JK, Tian C, Fleming GF, et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. Gynecol Oncol. 2010;116(3):301-6.
50. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975;42:101-4.
51. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170(4):974-9.
52. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002 Mar 1;20(5):1248-59.
53. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol. 2006;103(2):559-64.
54. Hoffman MS, Zervos EE. Colon resection for ovarian cancer: intraoperative decisions. Gynecol Oncol 2008;11:56-65.
55. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol. 2006.
56. Kim HS, Ju W, Jee BC, et al. Systematic lymphadenectomy for survival in epithelial ovarian cancer: a meta-analysis. Int J Gynecol Cancer. 2010;20(4):520-8.
57. du Bois A, Reuss A, Harter P, et al. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of three prospectively randomized phase III multicenter trials. J Clin Oncol. 2010;28(10):1733-9.
58. van der Burg ME, van Lent M, Buyse M, Kobierska A, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med. 1995;332(10):629-34.
59. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med. 2004;351(24):2489-97.
60. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943-53.
61. Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. Gynecol Oncol. 2007;104(2):480-90.
62. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med. 1996;334(1):1-6.
63. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst. 2000;92(9):699-708.
64. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2003;21(17):3194-200.
65. du Bois A, Lück HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst. 2003;95(17):1320-9.
66. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst. 2004;96(22):1682-91.
67. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol. 2009;27(9):1419-25.
68. Teneriello MG, Gordon AN, Lim P, Janicek M. Phase III trial of induction gemcitabine (G) or paclitaxel (T) plus carboplatin (C) followed by elective T consolidation in advanced ovarian cancer (OC): Final safety and efficacy report. J Clin Oncol 2010;28:18s, (suppl; abstr LBA5008).
69. NCI Clinical Announcement – Intraperitoneal chemotherapy for ovarian cancer. http://ctep.cancer.gov/highlights/docs/clin_annc_010506.pdf
70. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354(1):34-43.
71. Berry E, Matthews KS, Singh DK, et al. An outpatient intraperitoneal chemotherapy regimen for advanced ovarian cancer. Gynecol Oncol 2009;113(1):63-7.
72. Nagao S, Fujiwara K, Ohishi R, et al. Combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel in suboptimally debulked epithelial ovarian cancer. Int J Gynecol Cancer 2008;18(6):1210-4.
73. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335(26):1950-5.
74. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19(4):1001-7.
75. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374(9698):1331-8.
76. Burger RA. Role of vascular endothelial growth factor inhibitors in the treatment of gynecologic malignancies. J Gynecol Oncol 2010:3-11.
77. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25(33):5165-71.
78. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California,

Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 2008;26(1):76-82.
79. Cheng X, Moroney JW, Levenback CF, et al. What is the benefit of bevacizumab combined with chemotherapy in patients with recurrent ovarian, fallopian tube or primary peritoneal malignancies? J Chemother 2009;21(5):566-72.
80. Burger RA, Brady MF, Bookman MA, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. J Clin Oncol 28:18s, 2010 (suppl; abstr LBA1)
81. Perren T, et al. ICON7: A phase III randomised Gynaecologic Cancer InterGroup trial of concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab, versus chemotherapy alone in women with newly diagnosed epithelial ovarian (EOC), primary peritoneal (PPC) or fallopian tube cancer (FTC). ESMO 2010; (abstract LBA4)
82. Sabbatini P. Consolidation therapy in ovarian cancer: a clinical update. Int J Gynecol Cancer 2009;19 Suppl 2:S35-9.
83. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol 2003;21(13):2460-5.
84. Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. Gynecol Oncol 2009;114:195-8.
85. Cass I, Baldwin RL, Varkey T, et al. Cancer. 2003 May 1;97(9):2187-95. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 2003; 97(9):2187-95.
86. Köbel M, Kalloger SE, Boyd N, et al. Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. PLoS Med. 2008 Dec 2;5(12):e232.
87. Huhtinen K, Suvitie P, Hiissa J, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. Br J Cancer. 2009 Apr 21;100(8):1315-9.
88. Rustin GJ, van der Burg ME, Griffen CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Journal Clinical Oncology 2010; 376:1155-63.
89. Galaal K, Naik R, Bristow RE, et al. Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer. Cochrane Database Syst Rev 2010;6:CD007822.
90. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol 2009;112:265-74..
91. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-707.
92. Pujade-Lauraine E, Mahner S, Kaern J, et al. A randomized, phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG). J Clin Oncol 2009;27:18s (suppl; abstr LBA5509).
93. Sehouli J, Stengel D, Oskay-Oezcelik G, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: Results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2008;26:3176–82.
94. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-8.
95. Bookman MA, Darcy KM, Clarke-Pearson D, Boothby RA, Horowitz IR. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: A phase II trial of the Gynecologic Oncology Group. J Clin Oncol 2003;21:283-90.
96. Makhija S, Amler LC, Glenn D, et al. Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. J Clin Oncol 2010;28:1215-23.
97. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:5165-71.
98. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: A proof-of-concept trial. Lancet 2010;376:245-51.
99. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: Frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512-9.
100. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-34.
101. Sandhu SK, Wenham RM, Wilding G, et al. First-in-human trial of a poly(ADP-ribose) polymerase (PARP) inhibitor MK-4827 in advanced cancer patients (pts) with antitumor activity in BRCA-deficient and sporadic ovarian cancers. J Clin Oncol 2010;28:15s (suppl; abstr 3001)
102. Eitan R, Levine DA, Abu-Rustum N, et al. The clinical significance of malignant pleural effusions in patients with optimally debulked ovarian carcinoma. Cancer. 2005;103(7):1397-401.
103. Diaz JP, Abu-Rustum NR, Sonoda Y, et al. Video-assisted thoracic surgery (VATS) evaluation of pleural effusions in patients with newly diagnosed advanced ovarian carcinoma can influence the primary management choice for these patients. Gynecol Oncol 2010;116(3):483-8.
104. Fleming ND, Alvarez-Secord A, Von Gruenigen V, Miller MJ, Abernethy AP. Indwelling catheters for the management of refractory malignant ascites: a systematic literature overview and retrospective chart review. J Pain Symptom Manage. 2009;38(3):341-9.
105. Mystakidou K, Tsilika E, Kalaidopoulou O, et al. Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double- blind, controlled clinical trial. Anticancer Res. 2002;22(2B):1187-92.
106. Trompetas V, Saunders M, Gossage J, Anderson H. Shortcomings in colonic stenting to palliate large bowel obstruction from extracolonic malignancies. Int J Colorectal Dis. 2010;25(7):851-4.
107. Chi DS, Phaëton R, Miner TJ, et al. A prospective outcomes analysis of palliative procedures performed for malignant intestinal obstruction due to recurrent ovarian cancer. Oncologist 2009;14(8):835-9.
108. Kucukmetin A, Naik R, Galaal K, Bryant A, Dickinson HO. Palliative surgery versus medical management for bowel obstruction in ovarian cancer. Cochrane Database Syst Rev 2010;7:CD007792.

Part IV Surgical Atlas

31

Minimally Invasive Surgery in Gynecologic Oncology

Pedro T. Ramirez, Michael Frumovitz, Pedro Escobar

INTRODUCTION

Minimally invasive surgery is currently considered a safe and viable option in the management of most gynecologic malignancies. Compared to standard laparotomy, laparoscopic or robotic surgery is associated with lower blood loss and transfusion rates, lower intraoperative complication rates, decreased analgesic requirements in the immediate postoperative period, shorter length of hospitalization, lower postoperative complication rates, quicker return of bowel function, and improved short-term quality of life.

This chapter provides an overview of the standard laparoscopic procedures and robotic surgery. Details on the preoperative evaluation and postoperative care of patients undergoing the procedures described, and specific steps for the more commonly performed are provided. As the anatomical dissections are the same as for open procedures (Chapters 25 and 26), the illustrations and figures are limited to those aspects specific to the minimally invasive surgical approach.

LAPAROSCOPIC SURGERY

Cervical Cancer

Laparoscopic Radical Hysterectomy

Procedure Overview

Since the initial publications by Nezhat et al. [1] and Canis et al. [2], several retrospective studies have documented the safety and feasibility of total laparoscopic radical hysterectomy (TLRH), with a major complication rate of just 5% [3]. In a study by Frumovitz et al. [4], the authors compared 35 women who had undergone total laparoscopic radical hysterectomy (TLRH) to 54 women who had open radical hysterectomy (ORH) and found significantly less blood loss, shorter hospital length of stay and increased operative time for the TLRH group. Transfusion rates were low in both groups (15% ORH vs. 11% TLRH). Intraoperative and postoperative noninfectious complications were the same for both groups but the ORH group had a significantly higher postoperative infectious complication rate than the TLRH group (53% vs 18%). These complications included postoperative febrile morbidity, wound cellulitis, urinary tract infections, pneumonia, and intrabdominal abscesses.

In evaluating oncologic outcomes it appears that there is equivalency between TLRH and ORH. In their large series of 295 women who underwent TLRH, Chen et al. [3] reported overall disease-free survivals of 95% for women with stage IA disease.

Box 31.1 Master Surgeon's Corner

- Proper patient positioning with steep Trendelenburg will facilitate pelvic exposure and dissection.
- Develop the avascular para-vesicle and para-rectal spaces early in the course of operation to facilitate exposure to the parametria for ureteral dissection.

Preoperative Management

Patients with early-stage cervical cancer scheduled for a radical hysterectomy should routinely undergo a chest x-ray and type and cross. The use of other imaging modalities such as CT or MRI scans is not recommended, unless there is evidence to suspect metastatic disease.

All patients should undergo bowel preparation one day prior to surgery and antibiotic prophylaxis on the day of surgery. The choice of bowel preparation used by the authors is Half-lytely (polyethylene glycol) and the antibiotic regimen most frequently recommended is cefoxitin 2 grams intravenously. Although there is not a standard regimen for thromboembolic prophylaxis, patients should either undergo administration of subcutaneous heparin (5000 U) preoperatively or have compression devices used during the procedure and subsequently until ambulation.Surgical Technique

Initial Steps

After induction of general anesthesia, the patient is placed in the low lithotomy position using Allen stirrups. Typically, the patient's arms are tucked at her sides. Care must be taken to protect the patient's hands and fingers when the foot of the table is raised or lowered. *(Figure 31-1)* Monitors are placed at the foot of the table.

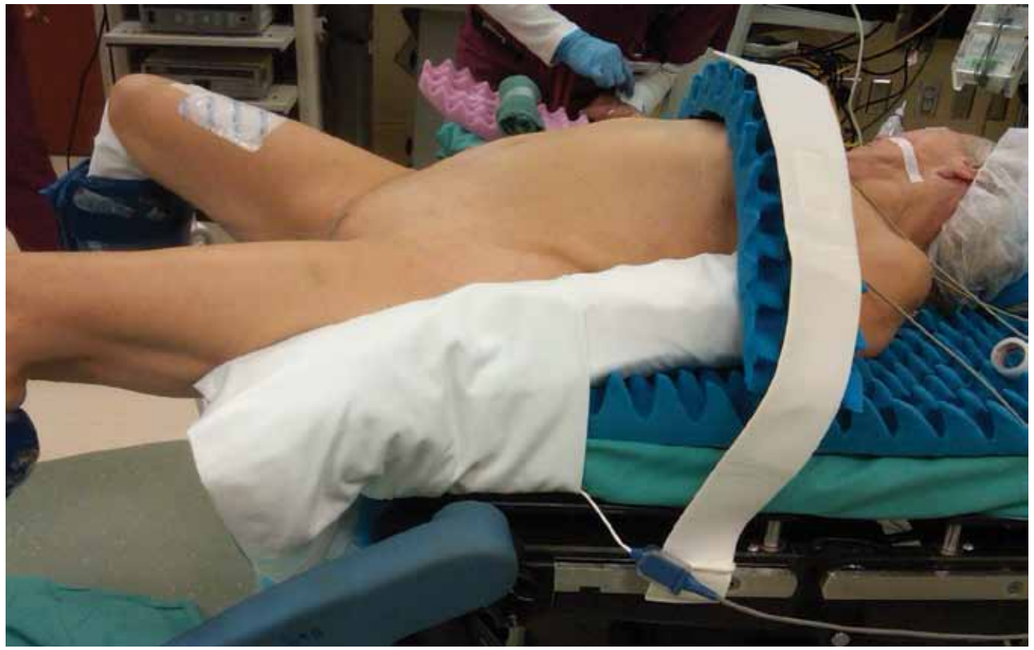

FIGURE 31-1. Patient positioning for laparoscopic surgery.

After the patient is prepared and draped, a Foley catheter is placed under sterile conditions. A sterile speculum is then placed into the vagina, and a single-toothed tenaculum is used to grasp the anterior lip of the cervix. A uterine manipulator is placed. The preferred uterine manipulator used by the authors is the V-Care manipulator (Conmed Endosurgery, Utica, NY).

Incision Placement

A 12-mm Xcel bladeless trocar (Ethicon Endo-Surgery, Cincinnati, OH) that incorporates a 0-degree laparoscope is placed at the level of the umbilicus and introduced into the abdominal cavity under direct visualization. In patients with a prior midline incision, the initial entry into the abdominal cavity is made approximately 2 cm below the left costal margin at the level of the midclavicular line to avoid injury to bowel adherent to the anterior abdominal wall. Once the trocar has been safely introduced into the abdominal cavity, the cavity is insufflated. The intra-abdominal pressure is maintained at 16 mm Hg. Two additional 5- or 12-mm Xcel bladeless trocars are placed in the right and left lower quadrants, and an additional 5-mm Xcel bladeless trocar is inserted in the midline above the pubic symphysis. *(Figure 31-2)*

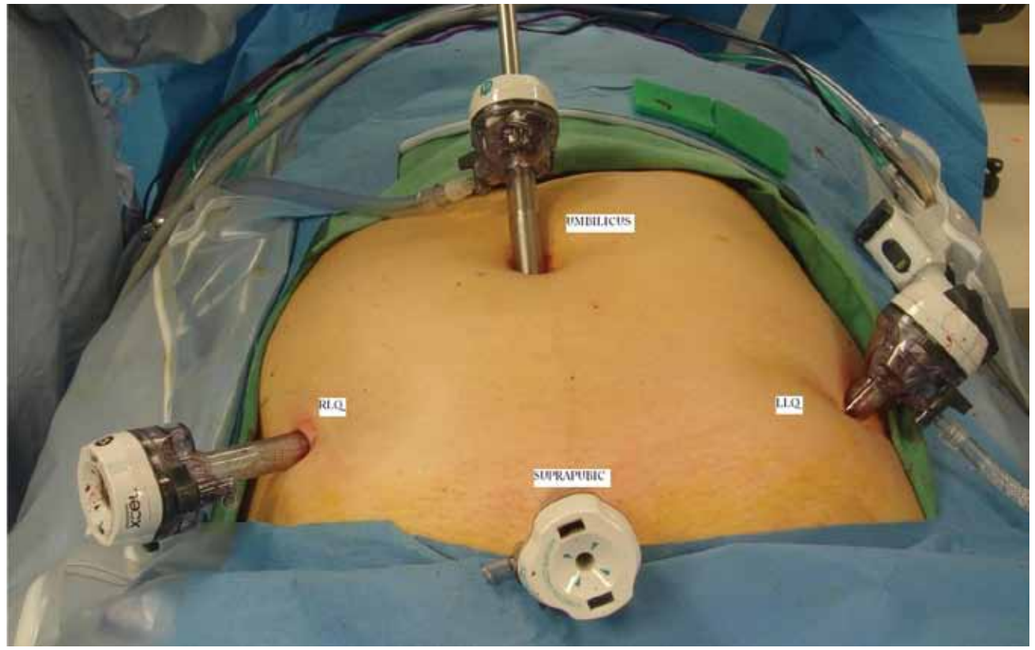

FIGURE 31-2. Patient positioning for laparoscopic surgery.

Retroperitoneal Exploration

The pelvis and abdomen are thoroughly explored to rule out intraperitoneal disease. The bowel is then mobilized into the upper abdomen, and the round ligaments are transected bilaterally. An incision is made in the peritoneum over the psoas muscle immediately lateral to the infundibulopelvic ligament. The infundibulopelvic ligament is retracted medially to permit identification of the ureter. The iliac vessels are also exposed at this time. The lymph-bearing tissue is then probed to rule out any obvious metastatic disease to the pelvic lymph nodes. Any suspicious nodes are removed and sent for frozen-section examination. Barring obvious lymph node metastasis, the pelvic lymph node dissection is completed after the radical hysterectomy.

Parametrial and Bladder Dissection

The paravesical space is dissected by following the external iliac vessels distally and placing medial traction on the superior vesical artery. The pararectal space is identified by dissecting between the internal iliac vessels and the lateral aspect of the ureter. Once these spaces have been created, one can easily identify the uterine vessels. After identification, the uterine vessels are transected at the point of origin from the internal iliac vessels. The uterine artery and vein are transected together. The bladder peritoneum is incised across the anterior aspect of the uterus and dissected down off the cervix. The bladder should be mobilized to below the level of the cup of the uterine manipulator to assure there is an adequate surgical margin of at least 1-2 cms. This can be performed by pushing the uterine manipulator cephalad with the uterus straight along its axis. We take particular care at this point in the procedure to completely separate the bladder fibers from the anterior vagina as this facilitates closure of the vaginal cuff at the end of the procedure.

The ureters are separated from their medial attachments to the peritoneum. The parametrial tissue is mobilized medially over the ureters. The ureters are unroofed to the point of their insertion into the bladder bilaterally. The lateral aspect of the vesicouterine ligament is then divided, and the bladder is further mobilized inferiorly to ensure adequate vaginal margins. The uterus is anteflexed using the uterine manipulator, and blunt graspers are used to apply counter traction across the posterior cul-de-sac. The peritoneum above the sigmoid colon and rectum is then incised, exposing the rectovaginal space. The attachments between the rectum and the vagina are cut

CHAPTER 31

in the midline, exposing the uterosacral ligaments. The uterosacral ligaments are then divided.

Circumferential Vaginotomy and Closure

Once the previously described procedures are complete, the cervix is now free of all its vascular and suspensory attachments and the specimen can be removed. A circumferential incision is made into the vagina along the ring of the uterine manipulator. The specimen is completely separated from the upper vagina and removed. The vaginal cuff is sutured laparoscopically.

Box 31.2 Caution Points

- Ensure that the patient's legs are properly positioned and hands protected to avoid inadvertent injury.
- Maintain direct visualization of the ureter when using thermal energy for parametrial dissection and division of vascular pedicles.

Postoperative Management

Patients undergoing laparoscopic radical hysterectomy are routinely placed on a demand intravenous analgesic pump and an oral analgesic regimen. All patients are ordered a regular diet on the evening of surgery. A Foley catheter is left in place postoperatively for a total of 5-7 days. A trial of void is attempted at that time and if the post-void residual is <150 mL, the catheter is removed. If the patient fails the voiding trial then the catheter is left in place for another week. We do not routinely recommend thromboembolic prophylaxis postoperatively in patients undergoing minimally invasive surgery. A study by Nick et al. [5] in patients undergoing laparoscopic surgery showed that the rate of a deep venous thromboembolism or pulmonary embolism was 0.7%.

Box 31.3 Complications and Morbidity

- Ureteral or bladder injury (1-3%)
- Delayed recovery of bladder function
- Port site hematoma or hernia

Laparoscopic Staging for Locally Advanced Cervical Cancer

Procedure Overview

Surgical staging of patients with locally-advanced cervical cancer remains controversial. An open transperitoneal approach is associated with high morbidity and mortality secondary to bowel complications, particularly when surgery is followed by radiotherapy. An extraperitoneal approach by laparotomy has been shown to decrease the complication rate from 30% to 2% compared with the transperitoneal approach. [6]

As many as 22% of patients with Stage IB2-IV cervical cancer and negative para-aortic lymph nodes on pre-operative CT or combined PET/CT imaging will be found to harbor metastatic disease in the para-aortic nodes when submitted to laparoscopic extraperitoneal staging [7]. These findings strongly argue for the consideration of surgical staging in patients with locally-advanced cervical cancer for diagnostic purposes. In addition, LeBlanc et al. [8] found a therapeutic effect from surgical staging of locally advanced cervical cancer. In their study of 184 patients with stages IB2-IVA cervical cancers, they found women with microscopic metastatic disease to the para-aortic lymph nodes had the same survival as those women who had pathologically negative lymph nodes.

Box 31.4 Master Surgeon's Corner

- Ureteral or bladder injury (1-3%)
- Delayed recovery of bladder function
- Port site hematoma or hernia

Preoperative Management

Patients scheduled to undergo surgical staging of locally advanced cervical cancer routinely undergo a PET/CT imaging evaluation. Alternatively, a CT scan of the chest, abdomen, and pelvis is recommended. Patients should have no evidence of metastatic disease prior to undergoing surgery. Routine bowel prep,antibiotic prophylaxis, and thrombo-embolic prophylaxis is recommended.

Surgical Technique

Initial Steps. The patient is placed in a supine position under general anesthesia with the right arm adducted and secured and the left arm placed at a right angle to the patient. A 5-mm endoscope is placed at the inferior margin of the umbilicus. The abdominal and pelvic cavity is inspected for intraperitoneal metastatic disease.

Development of Extraperitoneal Space. If the intraperitoneal inspection is clear, a 15-mm incision is made 3-4 cm medial and superior to the left anterior iliac spine. The skin, fascia, transverse muscles, and deep fascia are incised, with care taken not to open the peritoneum. The surgeon's left forefinger is introduced in the incision to free the peritoneal sac from the deep surface of the muscles of the abdominal wall under laparoscopic monitoring. A 10-mm balloon-tip trocar is then placed in the extraperitoneal space of the flank. The retroperitoneum is insufflated to a pressure not exceeding 15 mm of mercury. At the same time the peritoneal cavity is deflated. The laparoscope is then introduced through the balloon-tip trocar. A second 10-mm trocar is then introduced into the extraperitoneal space. The penetration point is located in the midaxillary line under the subcostal margin approximately 5 cm cephalad to and 3-4 cm lateral to the initial point. A 5-mm trocar is then placed 3-4 cm cephalad to this second 10-mm trocar. *(Figure 3)*

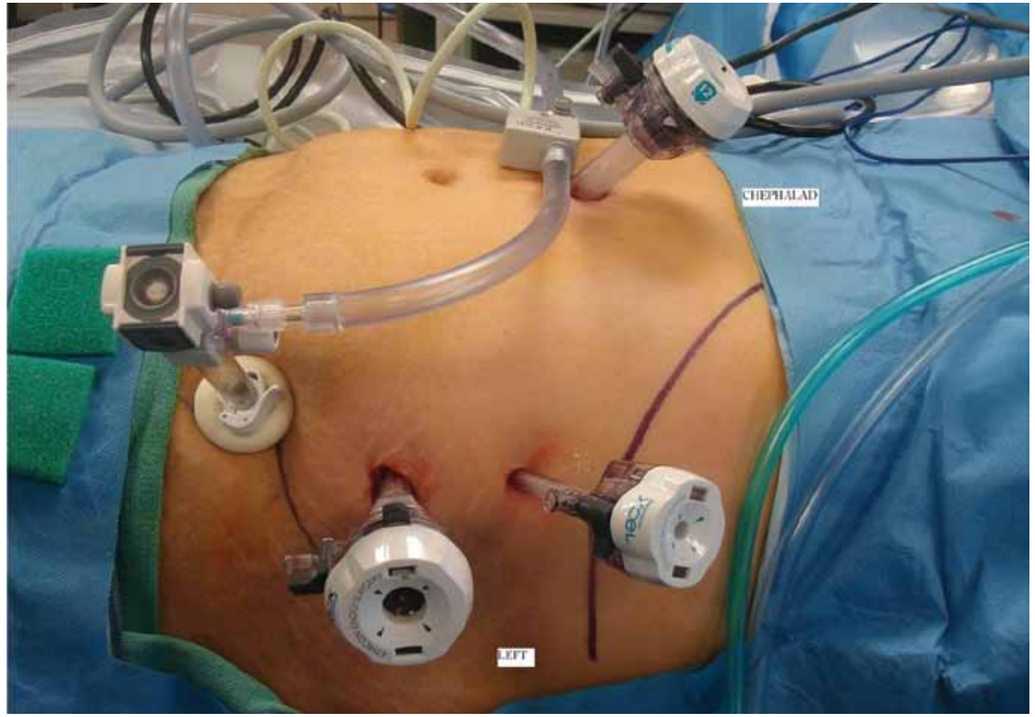

FIGURE 31.3. Trocar placement for extraperitoneal para-aortic lymphadenectomy

Removal of Common Iliac and Para-aortic Nodes. The dissection is performed bilaterally from the level of the common iliac vessels to the level of the left renal vein. (Figure 4) When there is evidence of grossly positive lymph nodes, these are sent to pathology for frozen section evaluation. If metastatic disease is confirmed, the laparoscopic procedure is aborted. At the completion of the procedure all patients have an incision performed in the peritoneum overlying the left para-colic gutter in order to minimize the likelihood of development of postoperative lymphocysts. If a patient is found to have a grossly positive node, then the incision on the peritoneum is not performed. This is to reduce the potential of spread of disease to the peritoneal cavity. No drains are placed at the completion of surgery.

Box 31.5 Caution Points

- Careful blunt dissection is required to avoid entering the peritoneal cavity when developing the extraperitoneal space.
- Ensure that the ureters are under direct visualization when using thermal energy to dissect nodal tissue.

Postoperative Management

This procedure is routinely performed as an outpatient procedure. No drains are placed at the completion of surgery. Most patients are placed on an oral analgesic regimen and are discharged from the hospital once they have voided and tolerated a regular diet.

CHAPTER 31

Generally patients are able to start treatment with chemotherapy and radiation within 14 days from their surgery.

Box 31.6 Complications and Morbidity

- Vascular injury
- Ureteral injury
- Retroperitoneal lymphocyst formation

Uterine Cancer

Simple Hysterectomy and Staging

Procedure Overview

The introduction of minimally invasive surgery as a treatment option for women with endometrial cancer began in the early 1990's with multiple reports of laparoscopic-assisted vaginal hysterectomy and lymph node staging. In 1996, the Gynecologic Oncology Group opened LAP-2, a randomized controlled trial assigning patients to laparoscopy or laparotomy in a 2:1 ratio. Upon completion, 2,516 patients were evaluable. [9]

As expected, operative time was longer in the laparoscopy group (204 minutes vs. 104 minutes) but hospital length of stay was shorter (3 days vs. 4 days). Only 52% of patients who underwent laparoscopy stayed > 2 days compared to 94% of those who had a laparotomy. There was no difference in intraoperative complications between the two groups although 26% of patients in the laparoscopy group required conversion to laparotomy. Grade 2 or greater postoperative complications were significantly higher in the laparotomy group compared to the laparoscopy group (21% vs. 14%).

Preoperative Management

Patients with a diagnosis of endometrial cancer routinely undergo a chest x-ray evaluation prior to surgery. If the patient has a preoperative diagnosis of a high-risk type of endometrial cancer such as papillary serous carcinoma, clear cell, or sarcoma then a more extensive evaluation such as a CT or MRI scan of the abdomen and pelvis is recommended.

Table 12-6 Relevant Randomized Control Trials in Early Stage Invasive Ovarian Cancer

Trial(s)/Author	Treatment arms	Overall Survival	Conclusions
Ovarian Cancer Study Group/GOG (Young, 1990)	Trial 1: Observation vs melphalan up to 12 cycles	Arm 1: 94% vs. 98%	No adjuvant therapy required in low risk early stage ovarian cancer.
	Trial 2: ^{32}P vs. melphalan up to 12 cycles	Arm 2: 78% vs. 81%	^{32}P or melphalan provide similar outcome in high risk early stage ovarian cancer.
GOG 95 (Young, 2003)	^{32}P vs cyclophosphamide/ cisplatin x 3 cycles	78% vs. 83%	Though no difference in survival, lower recurrence and complication rates justify platinum based chemotherapy as preferred treatment.
ACTION/ICON (Trimbos, 2003)	Observation vs. platinum based chemotherapy	74% vs. 82%*	Platinum based chemotherapy improved survival in high risk early stage ovarian cancer.
GOG 175 (Bell, 2006)	Paclitaxel/Carboplatin 3 vs 6 cycles	81% vs. 83%	Compared to 3 cycles, 6 cycles of paclitaxel and carboplatin did not significantly alter recurrence rate or improve survival and was associated with increased toxicity.
GOG157 (Mannel, 2010)	Paclitaxel/carboplatin x 3 cycles followed by observation vs 24 weeks of paclitaxel	85% vs. 86%	The addition of 24 weeks of paclitaxel did not improve survival in patients treated with 3 cycles of paclitaxel and carboplatin.

* $p < 0.05$