Practice Guidelines: Ovarian Cancer

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Ovarian cancer remains the leading cause of gynecologic malignancy mortality in the United States and is fourth overall in women behind lung, breast and colorectal cancer. Although significant advances have been made in the evaluation and treatment of ovarian cancer, the overall long-term survival has not changed significantly during the past 20 years. More than 70% of women have their disease diagnosed in advanced stages (III or IV) and have a 5-year survival less than 30%. Because of such grim statistics, effective secondary methods of treatment or preferably preventive approaches must be developed.

Screening

The 1994 National Institutes of Health (NIH) Consensus Conference on ovarian cancer concluded that there is no effective method for screening and detecting early ovarian cancer.

Diagnosis

The usual symptomatology associated with ovarian malignancies is that of advanced disease: abdominal pain, bloating, increasing abdominal girth, general digestive disturbances, abdominal and pelvic discomfort, and, at times, uterine bleeding. It is noted that all are essentially nonspecific and, once present, are most often associated with spread of malignancy throughout the abdominal cavity with involvement of the visceral and parietal peritoneal surfaces. When ascites or upper abdominal metastatic disease is present, bloating, heartburn, diminished appetite, nausea, and generalized discomfort are often the case. Stage I and lower pelvic disease may be detected by palpation of an asymptomatic mass or be associated with pelvic pressure and urinary frequency.

Diagnostic Techniques

Physical Examination

It has been estimated that routine pelvic examination will detect only 1 case of ovarian carcinoma in 10,000 asymptomatic women examined. Although the character of a mass found at the time of examination is not diagnostic, a unilateral, cystic mass that is mobile and less than 10 cm in diameter is more consistent with a benign process when compared to the solid, bilateral, fixed and larger lesion with cul-de-sac nodularity. Other physical findings are those that would be expected with the presence of abdominal disease, chiefly, ascites or a ballottable omental mass.

Radiographic and Other Studies

The evaluation of presenting symptoms of the pelvic mass would include other gynecologic disorders, such as leiomyomata, tubo-ovarian abscesses, endometriomas, gastrointestinal disorders, such as diverticular disease and neoplasia, and, rarely, urologic disorders, such as a pelvic kidney. In general, further diagnostic evaluation is directed toward the patient’s symptoms, physical examination, and general medical considerations, and may include some of the following: chest x-ray, intravenous pyelogram, barium enema and/or colonoscopy, upper gastrointestinal tract roentgenograms, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). While CT may not detect the presence of a gastrointestinal tract primary as well as barium enema or colonoscopy, the preoperative identification of parenchymal liver metastases, suprarenal lymphadenopathy, or extensive mesenteric disease by CT may influence the degree of intraoperative cytoreductive efforts.

The following tumor markers may be evaluated to be used for diagnostic and therapeutic response evaluations:

- Alpha-fetoprotein (AFP) is elevated in most endodermal sinus tumors, embryonal cell
carcinomas, or mixed germ cell tumors containing these elements and is useful not only in their diagnosis but in evaluating therapeutic response. Human chorionic gonadotropin (hCG) is elevated in patients with nongestational ovarian choriocarcinoma and may also be elevated in patients with dysgerminoma and embryonal cell carcinoma.

- Lactate dehydrogenase (LDH) may be of potential value in patients with ovarian dysgerminoma.

- CA 19-9 is potentially useful in following patients with mucinous ovarian carcinomas.

- Carcinoembryonic antigen (CEA) levels, although not specific for ovarian tumors, are sometimes found to be elevated in patients with mucinous ovarian tumors, and, hence, serial levels may prognosticate the clinical course, with rising values preceding clinical disease. If elevated initially, primary bowel cancer should be considered.

- CA-125 is known to be elevated in more than 80% of patients with epithelial ovarian malignancies, especially serous. CA-125 measurements may be useful in following the response to therapy and the presence of persistent or recurrent disease in women who had an elevation at the time of known disease. In postmenopausal women with a pelvic mass, an elevation of CA-125 greater than 65 U/mL is predictive of malignancy in up to 75% of cases. Benign conditions, such as uterine fibroids, endometriosis, or inflammatory or infectious processes, produce CA-125 elevations that limit the specificity of this tumor marker.

Radionuclide imaging utilizes radioisotopes chelated to antibodies directed against tumor-specific antigens. Although a promising research technique, its role in the diagnosis of preclinical disease and its usefulness in the follow-up of patients with disease is still under evaluation. Diagnostic paracentesis is generally not considered of definitive value since patients with ovarian malignant ascites will not always demonstrate malignant cells in diagnostic specimens. Paracentesis can, however, be performed in the selected patient to evaluate cirrhosis as an etiology for ascites or to relieve symptoms. Laparoscopy is helpful in evaluating patients with ovarian enlargement that is not well defined on pelvic examination and ill defined radiographically. Its role in the evaluation of patients with persistent symptomatology and negative diagnostic evaluation has been shown as well. Uncomplicated ovarian cysts satisfying benign criteria may be managed laparoscopically in selected cases. Its role in the actual management of malignancy without laparotomy, however, remains controversial and under evaluation. The use of diagnostic laparoscopy in the face of ascites or suspicious disease results in unnecessary anesthesia, morbidity, expense, and delay in initiating definitive therapy.

**Staging**

Appropriate determination of stage, or the extent of disease at the time of diagnosis, is of critical importance in the management of epithelial ovarian cancer, since both treatment and prognosis are strongly dependent on stage. Historically, inadequate assessment of stage has been a major problem in the management of patients with ovarian cancer. Unlike many other human malignancies, the staging system for ovarian cancer is based on the results of a properly performed surgical procedure, together with the results of clinical and histopathologic evaluations. The current staging system of the International Federation of Gynecology and Obstetrics (FIGO) is shown in Table 1. Appropriate determination of the stage of disease in patients with ovarian cancer requires a properly performed surgical procedure. Surgery generally involves exploratory laparotomy through a vertical abdominal incision to allow access to the upper abdomen. Peritoneal washings or ascites are obtained for cytologic analysis upon entering the abdomen. A complete and systematic exploration of the abdominal cavity from the diaphragms to the pelvic floor must be performed, and any suspicious areas biopsied. In patients who appear grossly to have
stage I or stage II disease, an infracolic omentectomy and sampling of aortic and pelvic lymph nodes are mandatory for complete staging. In these early stages, random peritoneal biopsies should also be performed from multiple areas, including the pelvis, pericolic gutters, and diaphragms. Clinically positive nodes should be excised to the maximum extent possible. Surgery should include hysterectomy, bilateral salpingo-oophorectomy, and omentectomy, except in selected patients with a well-differentiated tumor limited to one ovary, in whom it may be possible to preserve reproductive potential. A supracervical hysterectomy may be indicated in the presence of extensive carcinomatosis in the cul-de-sac.

A thorough preoperative discussion with the patient about the risks of staging laparotomy and her wishes regarding future childbearing are critical in surgical planning for ovarian cancer. The surgical goal should be optimal cytoreduction to less than 1 to 2 cm to optimize response to chemotherapy. A gynecologic oncologist, if available, should be consulted regarding the appropriate procedures and participate in the surgical staging. Studies in the United States and abroad have shown that ovarian cancer patients staged by a gynecologic oncologist have significantly smaller residual disease and improved survival compared to those operated on by nongynecologic oncologists.

**Treatment**

**Primary Surgery**

After the patient has been evaluated preoperatively, exploratory laparotomy is essential for definitive diagnosis and staging. The patient should be advised of the potential for malignancy based on the physical as well as imaging studies, and an explanation given with respect to the possible necessity for carrying out the additional surgical procedures involved in surgical staging. The patient should be prepared optimally with bowel preparation, prophylactic antibiotics, and prophylactic measures against venous thrombosis and embolism.

A key surgical principle is to remove as much tumor as is safely possible. After removal of the ovarian mass or masses and the frozen section reveals a malignant tumor, removal of the uterus and both tubes and ovaries is carried out unless mitigated by the patient’s reproductive status and extensive preoperative discussions. It is vital that any masses adherent to the pelvic peritoneum be approached by defining the retroperitoneal spaces, identifying the ureters, and removing the peritoneum along with the pelvic masses. This will reduce blood loss, permit more effective removal of the tumor, and reduce the risk of ureteral or blood vessel injury. In addition, omentectomy and removal of all gross cancer is carried out. The omental removal should be at least infracolic, depending on the extent of visible metastases to this structure.

Adherent areas of the primary tumor should be identified for adhesions and external excrescences. Any adhesions to the peritoneum should be biopsied specifically. There is currently an increasing trend to carry out more complete dissections of the pelvic and para-aortic nodes (i.e., lymph node dissection rather than sampling), particularly in patients with either early disease or optimal cytoreduction. The presence of extensive residual disease obviates the need for nodal dissection. Following completion of the procedure, an inventory of residual disease, including both the location and size, should be carried out in a systematic fashion and recorded in the operative notes.

Bowel resection during the primary debulking procedure is occasionally indicated if obstructive symptoms are present or complete cytoreduction is enabled. It is uncommon to see a primary ovarian cancer present initially with bowel obstruction, and the presence of ascites may increase the infectious risks of colonic resections.

In patients who have low malignant potential or *borderline* epithelial tumors, more conservative surgery may be used, especially in patients still desiring reproductive potential. Staging procedures (as described above) may be carried out with preservation of the uterus and the ovary/ovaries after the ovarian masses have been completely removed and the remaining tissue is grossly free of tumor.

Fertility preservation may also be achieved in women with germ cell tumors of the ovary or sex cord-stromal tumors, which are usually unilateral. Unilateral salpingo-oophorectomy is performed with preservation of the uterus and close inspection of the contralateral adnexa. With the effectiveness of multiagent chemotherapy, most of the germ cell tumors, including dysgerminoma, can be managed in a conservative fashion. Retrospective studies have shown no long-term impairment in fertility after conservative surgery followed by adjuvant chemotherapy, and the reliability of tumor markers in many germ cell tumors obviates the need for reassessment laparotomy.

**Chemotherapy**
Most epithelial tumors and all germ cell tumors (except grade 1, stage IA immature teratomas) require postoperative adjuvant chemotherapy. Other exceptions might be made in patients with selected grade 1, stage IA epithelial tumors. Clear cell tumors of all grades appear to be more likely to recur or metastasize than other epithelial tumors and may need to be dealt with more aggressively.

The evolving standard for adjuvant treatment of primary epithelial ovarian cancer in this country is paclitaxel (Taxol) combined with cisplatin (Platinol) or carboplatin (Paraplatin). The dose and scheduling options for paclitaxel are still under investigation. Selected early-stage/low-grade epithelial cancers may be treated with three or six courses of chemotherapy, and randomized clinical trials are in progress to define the duration of chemotherapy needed in these patients. Alkylating agents, such as cyclophosphamide (Cytoxan, Neosar), ifosfamide (Ifex), melphalan (Alkeran), and hexamethylmelamine (altretamine [Hexalen]) can be used for second-line or advanced-disease treatment. In the absence of definitive survival data, individualization in chemotherapy planning may selectively be done based on physician and patient preference.

Radiotherapy

The role of radiation therapy in the management of ovarian cancer at the present is limited but helpful in a small group of patients. Phosphorus-32 (32P) isotope has been used intraperitoneally in patients with stage I or early stage II disease after total removal of the primary tumor or in study settings after negative second-looks in advanced disease. The use of external-beam therapy as either whole-abdominal or pelvic irradiation has been used with mixed results, and whole-abdominal radiotherapy (WAR) as adjuvant therapy after cytoreductive surgery has not gained wide acceptance in this country. In the rare patient with isolated localized metastases, external therapy to a localized area may be indicated.

Special Considerations

An important feature with respect to ovarian carcinoma is the fact that not all patients who present with obvious findings relating to ovarian cancer, as described in the section above on diagnosis, will actually have a primary ovarian cancer. It has been reported that between 15% and 30% of patients presenting with bilateral pelvic masses actually have metastatic ovarian lesions from another organ. The greatest number come from the breast followed by the colon and finally from the endometrium and other organ sites. Breast examination and mammography as indicated, along with selective preoperative use of barium enema, colonoscopy, upper gastrointestinal series, CT scan, or the CEA tumor marker, may detect the presence of nonovarian primaries.

The second feature is that in young women with adnexal lesions and inconclusive pathologic diagnosis on frozen section, conservative surgery with preservation of the uterus and ovary, if uninvolved, should be considered. One may always return at a later time to carry out additional staging or surgical resection if the diagnosis is definitely cancer.

In pregnant patients with an adnexal lesion, exploration is carried out after the first trimester unless an obvious malignancy is suspected. Treatment of ovarian cancer in pregnant patients should be the same with respect to surgery and thorough staging as in nonpregnant patients. If the patient does not agree to surgery, definitive treatment may have to be delayed until the pregnancy is completed.

Platinum-based and multiagent chemotherapy have been used beginning in the second trimester without major reported complications.

Familial Ovarian Cancer

Another area that needs to be considered is the familial ovarian cancer syndromes. Patients with ovarian cancer in their family need a pedigree determination and can then be given a risk profile. With no history of ovarian cancer, the lifetime risk of ovarian cancer is 1 in 70. With one first-degree relative, the risk increases to 1 in 25 to 30. In pedigrees that demonstrate autosomal dominant inheritance for site-specific ovarian cancer, the risk is as high as 40% (50% transmission with 80% penetrance).

During the past few years, efforts have been made to isolate specific genes responsible for various familial ovarian cancer syndromes. Recently, mutations of the BRCA1 gene have been linked to 40% to 50% of early-onset hereditary breast cancers families and 80% to 90% of breast-ovarian cancer families. Somatic BRCA1 mutations have also been found in 10% of sporadic ovarian cancers. The lifetime risks for developing cancer based on BRCA1 mutation are 80% to 90% (breast) and 60% (ovary), as well as a three- to fourfold increased risk of colon and prostate cancer. The strong predictive value of BRCA1 mutation makes BRCA1 testing a potentially useful adjunct in the evaluation of women at risk for ovarian cancer.
Further developments in the molecular analysis of BRCA1 mutations may offer even more precise information for the counseling and management of affected women. Mutations in BRCA1 upstream of exon 13 are associated with a 1:2 breast-ovarian cancer distribution, while mutations downstream from exon 13 are associated with a 5:1 breast-ovarian ratio. A specific BRCA1 mutation, 185delAG, has been identified in 1% of Ashkenazi Jews, and 45% of the cancers that develop in affected women are ovarian, making this ethnic group a particularly important target group for BRCA1 screening and consideration for prophylactic oophorectomy.

In the absence of genetic testing information, prophylactic (bilateral) oophorectomy must be recommended as an indicated procedure to all women from high-risk families after childbearing or the age of 35 to 40 at the latest. In addition to ovarian cancer prevention, prophylactic oophorectomy also offers breast cancer protection in women with breast-ovary and Lynch II family cancer syndromes.

**Follow-up After Treatment**

Secondary surgery has been used as a “second-look” or “reassessment” operation to determine the response to therapy and whether or not to continue with further treatment. This procedure is limited to those in whom there is no evidence of persistent disease by physical examination, tumor markers, or scans, and it has not been found to be of any major benefit in patients with early stage I or stage II disease. The patient who may benefit most from second-look laparotomy is the partial responder with otherwise negative tumor markers and CT scan. These individuals, often with microscopic residual disease, may benefit from additional treatments when they would otherwise have been followed until more advanced disease became evident.

Post-treatment follow-up usually consists of a careful physical examination on a regular basis, usually every 3 months the first 2 years, then every 4 months in years 3 to 5, and every 6 months after 5 years. Thorough abdominal and pelvic/rectal examinations are mandatory. If elevated at the time of initial treatment, CA-125 may be used in follow-up. Scanning techniques, such as CT, MRI, and ultrasonography, may also be of some help. As mentioned above in the section on diagnosis, radionuclide imaging techniques are also being investigated as potentially more sensitive and specific indicators of disease status to aid in post-treatment follow-up.

**Treatment of Recurrence**

**Surgery**

Recurrent ovarian cancer is defined as disease that is detected at least 6 months after complete remission from primary therapy. While cytoreductive surgery is considered standard in the initial management of ovarian cancer, the role for secondary surgical debulking is less clear. When disease recurs or progresses within 6 months of primary chemotherapy, surgical cytoreduction appears to provide minimal benefit. Limited retrospective evidence, however, does suggest that surgical cytoreduction may improve survival as length of time to recurrence increases.

Major surgical interventions for recurrent and progressive ovarian cancer may be performed to provide relief of symptoms or improve quality of life. Intestinal obstruction is a common problem in women with advanced or recurrent ovarian cancer. Although some patients may be managed conservatively with fluid and electrolyte replacement, the majority of patients will require surgery to relieve the obstruction. The decision to operate depends on the surgeon’s assessment of the risks of surgery, as well as the patient’s life expectancy. Surgery for intestinal obstruction in this scenario improves survival at best by only a few months. However, more than 50% of patients can be expected to have improvement, as measured by the ability to leave the hospital. In some patients with diffuse carcinomatosis, palliation may be obtained with the use of either a surgically or percutaneously introduced gastrostomy tube.

**Chemotherapy**

The likelihood of a response to second-line chemotherapy in ovarian cancer is influenced by the initial response to chemotherapy, as well as the interval to recurrence. Response rates of 25% to 77% have been recorded in patients with a treatment-free interval of 6 months or more. The longer the treatment-free interval, the greater the response rate. This is true for retreatment with a platinum-based regimen or for other drugs, such as ifosfamide, hexamethylmelamine, and tamoxifen (Nolvadex), which have shown modest activity in phase II trials.

Currently, paclitaxel appears to be the most active agent in patients who have progressed on cisplatin. In addition, dose-intense salvage regimens with cisplatin and carboplatin have been reported with response rates in the 30% range. Although high response rates (70% to 80%) have
been reported with dose-intense therapy using autologous bone marrow and peripheral stem-cell support, long-term follow-up is lacking, and a survival benefit has yet to be demonstrated. The FDA has recently approved topotecan (Hycamtin) for second-line therapy in ovarian cancer based on promising clinical trials that demonstrate equal or superior activity to paclitaxel in the salvage setting.

Liposome-encapsulated doxorubicin (Doxil) offers an enhanced therapeutic ratio and is another promising agent being developed for ovarian cancer. Combinations of these agents with platinum are currently being investigated.

Patients with recurrent disease who are not responsive to treatment with standard chemotherapy may be considered for experimental protocols, including high-dose therapy, new chemotherapeutic agents, and immunotherapy. Protocols involving gene or antigene therapy will likely be available in the near future.

The information in the Society of Gynecologic Oncologists clinical practice guidelines should not be viewed as a body of rigid rules. The guidelines are general and are intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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References:

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