Management of Early Ovarian Cancer

Review Article [1] | March 01, 2004
By Yukio Sonoda, MD [2]

Epithelial ovarian cancer is the leading cause of death from gynecologic malignancies in the United States due, in large part, to the advanced stage at which it is commonly diagnosed. However, approximately one-third of cases are discovered at an early stage, when tumor is limited to the pelvis. Certain prognostic factors have been identified, which place patients with early disease at risk for recurrence and warrant the use of adjuvant therapy. Systemic chemotherapy remains the most commonly used adjuvant therapy in this setting, and several randomized European trials have recently suggested a benefit to its use. These studies, however, suffered from the lack of comprehensive staging, which must be considered when interpreting the literature on early stage disease. Ideally, these patients should have access to a gynecologic oncologist prior to their initial surgical procedure.

Ovarian cancer consistently ranks as the number 1 cause of death from gynecologic malignancies in the United States. In 2003, an estimated 25,400 new cases of ovarian cancer were diagnosed and approximately 14,300 women died from the disease. The death total exceeds that of all other gynecologic cancers combined, due in large part to the advanced stage at which the majority of ovarian cancers are diagnosed. For purposes of this review, early stage ovarian cancer can be classified as disease that has not spread beyond the true pelvis; ie, International Federation of Gynecology and Obstetrics (FIGO) stage I or II (Table 1). Early stage ovarian cancer comprises approximately one-third of all cases of the disease and is associated with a 5-year survival rate ranging from 66% to 90%. Early-stage ovarian cancer can be further subclassified based on the need for adjuvant therapy. The risk of recurrence is defined by certain prognostic factors, and although several clinicopathologic factors have consistently proven to place a patient at risk of relapse, there is disagreement about some factors. Controversy also continues as to what constitutes optimal treatment. This article focuses on epithelial ovarian cancers, which comprise the majority of ovarian cancers. Unfortunately, many studies of early-stage ovarian cancer are limited by inadequate staging and may overestimate the incidence of early disease while underestimating prognosis. In addition, the unrecognized inclusion of borderline tumors could potentially skew results. Development of Ovarian Cancer Epithelial ovarian cancer is believed to originate from the single layer of surface epithelium that covers the ovary. Disruption of this layer during ovulation may lead to invagination and result in cystic ovarian growths. Molecular genetic and morphologic techniques have provided evidence in support of this hypothesis. Examination of stage I ovarian carcinomas has demonstrated that they contain inclusion cysts with a morphologic continuum of normal epithelium, dysplastic epithelium, and invasive carcinoma. Further evidence that epithelial inclusions may be the origin of ovarian carcinoma has also been demonstrated on the genetic level. Using laser capture microdissection and microarray technology, Leitao et al showed that the gene expression profiles of ovarian cystic epithelium were significantly different from those of surface epithelial cells. They identified 126 genes that were differentially expressed in cysts compared to surface epithelium, with upregulation of cancer-specific antigens and putative oncogenic factors, downregulation of putative tumor suppressors, and altered expression of numerous genes associated with invasive disease. These data support the theory that epithelial inclusions represent a likely site of origin of ovarian cancer.
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FIGO = International Federation of Gynecology and Obstetrics.
Disease Spread

At a certain point, ovarian cancer cells will spread beyond the confines of the ovary. This is believed to occur by either direct extension, exfoliation of cells into the peritoneal cavity, lymphatic spread, or hematogenous dissemination. Ovarian cancer will eventually violate the ovarian capsule and spread directly to adjacent organs. In addition, once the capsule has been disrupted, exfoliated viable cells can be transported throughout the peritoneal cavity by normal peritoneal fluid and can implant on the parietal and visceral peritoneal surfaces, resulting in carcinomatosis. Lymphatic spread of ovarian cancer is believed to follow the vascular drainage of the ovary. In particular, the right ovarian vein drains directly into the inferior vena cava, and the left drains into the left renal vein. Lymphatic drainage from the ovary also occurs via the broad ligament and can lead to nodal disease in the pelvis. On occasion, spread via the round ligament can lead to involvement of the inguinal lymph nodes. Finally, hematogenous spread can result in liver, lung, central nervous system, or bone metastases. An understanding of the potential routes of spread is essential prior to undertaking a search for extraovarian spread of disease.

Staging of Ovarian Cancer

The importance of properly staging ovarian cancer cannot be overemphasized, given that adjuvant chemotherapy is recommended to treat all but the earliest stages of disease. The current FIGO staging system for ovarian cancer is based on a comprehensive surgical evaluation of the abdomen and pelvis and the spread pattern of the disease. Any surgeon who is confronted with an ovarian mass must be prepared to perform a staging procedure. The critical elements of the staging procedure are listed in Table 2.

Inadequate Staging

Despite the importance of the primary surgical exploration, the procedure is performed in many women by a general obstetrician/gynecologist or general surgeon. McGowan et al demonstrated that nearly half of 291 patients who underwent surgical exploration for ovarian cancer had incomplete documentation of stage at initial laparotomy.[5] When the data were analyzed by specialty, only 35% of general surgeons and 52% of general obstetricians/gynecologists documented a complete staging procedure, compared to 97% of gynecologic oncologists. However, only 12% of patients had their initial surgery performed by a gynecologic oncologist. Trimbos et al also illustrated the problem of improper staging of early-stage ovarian cancer.[6] In this series from the Netherlands, 59 patients underwent their initial surgical procedure at a peripheral hospital, and only 9 (15%) had a comprehensive staging procedure. The majority of patients were operated on by a general gynecologist/obstetrician, and 2 (5%) of 43 were deemed as having undergone a complete staging procedure. When a general gynecologist performed the procedure with a vascular surgeon, 38% (5/13) had a complete procedure. Difficult, potentially morbid components of the staging procedure that were most commonly not performed were the diaphragmatic biopsies and sampling of the retroperitoneal lymph nodes. Surprisingly, simple, nonmorbid portions of the staging procedure, such as peritoneal biopsies, were also omitted. The authors concluded that a lack of surgical skill and a lack of knowledge about potential sites of spread were equally responsible for the incomplete staging in this series. Recent reports from the National Institutes of Health (NIH) indicate that only...
9% of patients with early-stage ovarian cancer are treated appropriately. The NIH has recommended that women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer be given the option of having their surgery performed by a gynecologic oncologist. In addition, the Society of Gynecologic Oncologists recently issued their guidelines for referral to or consultation with a gynecologic oncologist (Table 3). Thorough surgical staging will reveal that a significant portion of patients with suspected early-stage disease actually have more advanced disease. Young et al demonstrated that as many as 31% of women with suspected early-stage disease will be upstaged after undergoing additional procedures. The majority (77%) of patients in this series who were upstaged were found to have stage III disease. Of these, 66% had their disease detected by procedures other than second laparotomy. The use of alternative approaches to staging will be reviewed.

### Table 3

**Society of Gynecologic Oncologists Guidelines for Referral to a Gynecologic Oncologist**

- Evidence of advanced disease: pelvic mass with omental caking, presence of effusion or ascites
- Diagnosis of a clinically suspicious pelvic mass (large > 10 cm, complex, fixed, nodular, bilateral)
- Premenarchal girls requiring surgical treatment for a pelvic mass
- Postmenopausal women with suspicious ovarian masses or elevated tumor markers
- Perimenopausal women with ovarian masses, particularly when associated with elevated CA-125
- Young patients with a pelvic mass and elevated tumor markers (CA-125, alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG])
- Suspicious findings present on imaging studies
- Presence of complex masses with solid components or ex crescences, or otherwise suspicious for cancer
- Suspicious pelvic masses found in women with a significant family or personal history of ovarian, breast, or other cancers (one or more first-degree relatives)

### Surgical Approaches Minimally Invasive Surgery

Despite the fact that laparotomy remains the standard approach to the management of most major gynecologic malignancies, over the past decade there has been a dramatic move toward incorporating minimally invasive surgery into the practice of gynecologic oncology. Better technology and improved operator skills have made many of the procedures that once required large abdominal incisions feasible with a minimally invasive approach. Decreased morbidity and hospital stay are some of the attractive features of minimally invasive surgery.

- **Feasibility of Laparoscopy** - The use of laparoscopy in the management of early ovarian cancer was first cited in a case report. Unfortunately, a comprehensive staging procedure was not performed. Querleu and Leblanc first described the complete laparoscopic staging of ovarian cancer patients. They described the procedure in nine patients who had initially undergone incomplete staging. Of these nine patients, seven were presumed to have stage Ia disease and underwent surgery for staging purposes; two patients, who obviously had stage III disease at the time of initial surgery, were comprehensively staged during their secondlook procedure. In this report, laparoscopic staging comprised infrarenal para-aortic lymphadenectomy, peritoneal cytology, and multiple peritoneal biopsies. Omentectomy, appendectomy, pelvic lymphadenectomy, contralateral salpingo-oophorectomy, salpingectomy, and/or laparoscopically assisted vaginal hysterectomy were performed, if
they had not been done previously. The mean total operative time was 227 minutes (range: 130-360 minutes), and the mean time for the paraaortic node dissection was 111 minutes (range: 65-240 minutes). Mean para-aortic node count was 8.6 (range: 5-17), and only one patient was found to have microscopic disease on the right diaphragm. No major intraoperative complications occurred, and the mean hospital stay was 2.8 days (range: 1-5 days). These authors suggested that laparoscopy may be an acceptable alternative to a restaging laparotomy; however, they cautioned that this approach should only be undertaken by an accomplished surgeon trained in gynecologic oncology and laparoscopy.

Childers et al reported on the laparoscopic staging of 14 patients with presumed stage I disease.[12] The staging consisted of pelvic and paraaortic lymphadenectomy, omentectomy, and washings. A hysterectomy was performed in five patients, and eight patients (57%) were upstaged based on operative findings: two to stage IC, three to stage II, and three to stage IIIC. Childers and his colleagues reported two perioperative complications, neither of which required conversion. The mean hospital stay was 1.6 days. The authors concluded that laparoscopic staging appeared to be an accurate technique that required further validation. Other groups have also demonstrated the feasibility of this staging procedure in patients with suspected early disease.[13] Recently, Leblanc et al updated their series in 28 patients with apparent stage I invasive ovarian cancer who underwent laparoscopic staging after an inadequate initial procedure (n = 25) or full laparoscopic management at initial surgery (n = 3).[14] The mean operative time was 230 minutes, and the mean hospital stay was 3.3 days. The median pelvic and para-aortic node counts were 13.7 and 19.7, respectively. One patient required conversion to laparotomy secondary to adhesions, and one pelvic abscess developed after appendectomy. Of 28 patients, 6 were upstaged, and of the 22 pathologic stage IA patients, 1 (4.5%) recurred at 4 years.

- **Laparoscopy vs Laparotomy**—Although many of the technical aspects of the staging procedure have been shown to be feasible, the question remains as to whether laparoscopy can produce results similar to those of laparotomy. Critics of laparoscopic staging cite loss of the ability to palpate and inspect the entire abdominal cavity.[15] The Gynecologic Oncology Group (GOG) has completed a phase II study (protocol 9302) of the feasibility and adverse effects of laparoscopic staging of early-stage ovarian, tubal, or peritoneal cancer. Results are pending, but hopefully this will begin to clarify the role of laparoscopy in the management of early-stage ovarian cancers. Currently, laparotomy is considered the standard staging approach to early-stage disease, and patients should be so informed during their presurgical consultation.

- **Hand-Assisted Laparoscopy**—A new technique that has recently become available is called hand-assisted laparoscopic surgery (HALS). This technique employs a port that allows the surgeon to insert one hand into the abdominal cavity while maintaining the pneumoperitoneum. Although this requires a larger incision than traditional laparotomy,
tactile sensation is restored. Krivak et al have reported on the use of this technique in ovarian cancer.\[16\] The authors studied 25 patients who were either staged or cytoreduced using HALS. Three patients with advanced-stage disease required conversion to traditional laparotomy to optimize cytoreduction. The procedure was also used to stage seven patients referred with unstaged disease. Procedures reported included hysterectomy, modified radical hysterectomy, bilateral salpingooophorectomy, omentectomy, pelvic and para-aortic node dissection, appendectomy, small bowel resection, partial colectomy, and low anterior resection. With a mean hospitalization of 1.8 days (range: 1-8 days), the authors concluded that this was a feasible alternative to laparotomy in carefully selected patients. The use of this technique warrants further investigation in the management of ovarian cancer.

**Conservative Surgery**

Although epithelial ovarian cancer is a disease of the postmenopausal population, it can occur in younger patients for whom the preservation of fertility is an issue. In fact, 7% to 8% of all malignant stage I epithelial cancers of the ovary occur in women less than 35 years old.\[17\] The standard surgical therapy for ovarian cancer would render these women infertile; thus, several studies have examined the role of conservative surgery in the management of early-stage ovarian cancer. Schilder et al reported the multiinstitutional experience in patients with stage IA and IC epithelial ovarian cancer who were treated with fertility-sparing surgery.\[18\] They identified 52 patients (42 stage IA, 10 stage IC) who had undergone unilateral oophorectomy and surgical staging; 20 patients also received adjuvant chemotherapy. With a median followup of 68 months, five recurrences were recorded, of which three developed in the remaining ovary. Two patients died of disease, and the 5-year survival rate was estimated to be 98%. Of the 24 patients who attempted conception, 17 were successful, with 26 full-term deliveries and 5 spontaneous abortions. The authors concluded that fertility-sparing surgery should be considered a treatment option for patients with stage I disease who wish to bear children. The survival of patients with early-stage epithelial ovarian cancer who have undergone fertility-sparing surgery has been compared to that of patients who have undergone hysterectomy and bilateral salpingooophorectomy in addition to staging. In a retrospective review, Brown et al identified 16 patients under age 40 with stage I epithelial ovarian cancer, who had undergone preservation of the contralateral ovary and hysterectomy at the time of surgical staging.\[19\] Of these women, 37% received adjuvant platinum-based chemotherapy due to high-risk features. At a median follow-up of 66 months (range: 1-174 months), 14 patients (88%) were alive and disease-free. Two of the 16 patients developed a recurrence in the retained ovary and died of their disease.

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<th>Clinicopathologic Prognostic Factors for Early-Stage Ovarian Cancer</th>
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<td>Rubin et al, 1993[30]</td>
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<td>Zanetta et al, 1998[31]</td>
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<td>Vergote et al, 2001[35]</td>
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*1988 FIGO stage.

**FIGO = International Federation of Gynecology and Obstetrics.**

Over the same time period, 92 patients with stage I disease underwent hysterectomy and bilateral salpingooophorectomy in addition to staging.\[19\] Of these 92 patients, 80 (87%) were alive without disease. There were eight successful pregnancies among five patients treated with fertility-sparing surgery. The authors concluded that fertility preservation in stage I patients is possible after comprehensive staging and does not appear to decrease survival. The subject of fertility preservation, however, remains controversial for this group of patients. These women should be counseled on the importance of comprehensive staging and the possibility of fertility preservation,
and this conservative approach should be limited to patients who meet certain criteria (Table 4). Furthermore, controversy exists as to whether patients with grade 2 tumors should be managed with conservative therapy.[15,20] Second-Look Surgery

Second-look surgery is a systematic surgical exploration in an asymptomatic patient who has completed a planned course of chemotherapy for ovarian cancer. Its use has been evaluated in patients with early-stage disease. Walton et al reported on 112 patients with FIGO stage I/II ovarian carcinoma who underwent secondlook surgery after completion of adjuvant therapy in an Ovarian Cancer Study Group/GOG trial.[21] Of the 95 patients who were asymptomatic at 18 months, only 5% had positive findings compared to 53% of the 17 patients who were symptomatic (eg, bowel obstruction, abdominal or pelvic complaints, weight loss, or other symptoms suspicious for recurrent disease). In a smaller series, Rubin et al reported on 54 stage I patients who underwent second-look surgery following complete surgical staging and adjuvant chemotherapy.[22] They, like Walton et al, found that only 5.5% had disease.[22] None of the patients with grade 1 tumors had disease. Tumor grade was a significant predictor of recurrence following a negative second-look procedure, with grade 1/2 tumors associated with a 0% risk of recurrence compared to a 52% risk for grade 3 tumors. Substage, histologic type, and chemotherapy type or duration did not predict recurrence. Given the small positive yield of second-look surgery in early-stage patients who have been comprehensively staged initially, this strategy is not routinely recommended. Prognostic Factors

Clinical Factors

Adjuvant treatment is usually recommended for all but the earliest-stage tumors, which reinforces the importance of precise surgical staging. Individual clinical, pathologic, and molecular factors have been studied to help identify patients with early-stage disease who are at low or high risk for relapse and who may or may not benefit from chemotherapy. However, many of these studies included patients who underwent incomplete staging and were treated with a variety of adjuvant modalities. Dembo et al conducted a two-part study to identify prognostic factors for relapse in patients with stage I epithelial ovarian cancer.[23] In the first phase, they reviewed the experience of 252 patients with stage I disease from the Princess Margaret Hospital in Canada. Tumor grade (grades 2/3) and dense adhesions were predictive of relapse. The second phase of the study was conducted to validate these newly identified factors in a second population of 267 patients from the Norwegian Radium Hospital. In this second analysis, tumor grade, dense adhesions, and largevolume ascites (>250 mL) were predictive of relapse. The authors concluded that tumor grade, adherence, and probably large-volume ascites were the only factors of prognostic significance in nonmetastatic ovarian cancer. Similarly, in an attempt to identify prognostic factors for the natural course of early-stage disease, Ahmed et al prospectively followed 194 patients with untreated stage I ovarian cancer.[24] Adequate surgical staging, which did not routinely include nodal sampling, was performed in 53% of the patients. Patients were classified as having unfavorable risk factors if they had stage IC disease, or IA/B disease with clear-cell or poorly differentiated tumors. Stage IA/B of serous, endometrioid, or mucinous histologic types, and grade 1/2 tumors were considered favorable. On multivariate analysis, histologic grade, ascites, and surface tumor were significant predictors of relapse, whereas FIGO substage was not.[24] These predictors of relapse were not significant predictors of survival, although there was a trend toward a worse survival among patients with these three predictors of relapse. The authors suspected that the lack of significance may have been due to the relatively small number of events. Although intraoperative rupture was not found to be prognostically significant, the impact of preoperative rupture remained unclear. In a large multi-institutional study, Vergote et al reviewed the outcome in 1,545 patients from six countries with stage I tumors and correlated disease-free survival with various clinical and pathologic variables.[25] All patients underwent laparotomy, hysterectomy, bilateral salpingooophorectomy, and infracolic omentectomy. Peritoneal washings, diaphragmatic scrapings, and retroperitoneal lymphadenectomy were not routinely performed. Tumor rupture and its timing were recorded. On multivariate analysis, degree of differentiation (moderate and poor), preoperative and intraoperative rupture, and age at diagnosis were predictive of recurrence. The study spanned a period in which 1973 FIGO staging criteria were employed. However, when patients were classified according to the most recent FIGO staging guidelines, substage was not predictive of relapse. Other retrospective studies have examined certain clinical prognostic factors in patients with early-stage ovarian cancer (Table 5).[23-31] In agreement with the studies cited above, histologic grade has been repeatedly identified as an independent factor in survival on multivariate analysis.[23-25,28-31] Some studies also cited clear-cell histology as a factor associated with poor prognosis.[27,29] Employing these clinicopathologic prognostic factors, a low-risk group of early-stage ovarian cancer patients can be defined that would probably not benefit from adjuvant therapy. This includes patients with FIGO...
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stage IA/B, grade 1 tumors.[32] Additionally, patients with high-risk factors should be offered some form of adjuvant therapy. For an intermediate- risk group of patients with FIGO stage IA/B, grade 2 tumors, adjuvant therapy remains controversial (Table 6).[8,15,27,33] Additional Prognostic Factors

It has been shown that there can be a fair amount of interobserver diagnostic variability in the interpretation of epithelial ovarian cancer.[34] In addition to clinical prognostic factors, attempts have been made to identify more objective factors that may be insightful about the prognosis of early stage ovarian cancers. Morphometric features and cellular DNA content have been studied.

- **DNA Ploidy**- Vergote et al studied the prognostic factors in 279 patients with invasive stage I ovarian cancer.[29] Patients were evaluated for clinicopathologic factors, as well as DNA ploidy, which were measured by flow cytometry. The 5-year crude and disease-free survival rates were 80% and 78%, respectively. No relapses occurred among the 77 patients with well-differentiated DNA diploid tumors, and 62 relapses occurred in the remaining 202 patients, of which 136 had nondiploid tumors. After multivariate analysis, degree of differentiation, DNA ploidy, and 1986 FIGO stage were prognostic factors in graded tumors. DNA index—a measure of the degree of aneuploidy—was not of prognostic value in this series.

- **Alternative Prognostic Factors**- Brugghe et al examined quantitative factors in 102 FIGO stage I patients treated with surgery alone.[35] Factors such as volume percentage of epithelium, mitotic activity index, mean nuclear area, and mean nuclear volume, were compared to clinical features. (Volume percentage of epithelium denotes the portion of neoplastic epithelium in a microscopic field. The mitotic activity index indicates the number of mitotic figures within the neoplastic epithelium in a defined number of high-power fields. Mean nuclear area is obtained by measuring 100 epithelial cancer nuclei in 100 fields of view, and the mean nuclear volume is calculated using stereologic techniques.) Median followup in the study was 54 months. FIGO stage and grade had significant prognostic value but histology did not. Mean nuclear area and mean nuclear volume were also shown to be significant prognostic factors. The 6-year overall survival was 100% in patients with a mean nuclear area of less than 55.6 μm² and 69% in patients with a mean nuclear area greater than 55.6 μm². No patients with a mean nuclear volume less than 460 μm³ died, compared to a 70% 6-year survival rate among those with a greater value. Mitotic activity index and volume percentage of epithelium did not show significant prognostic value. A multivariate combination of mean nuclear area and FIGO substages called the early carcinoma of the ovary prognostic score had the strongest prognostic value. The authors demonstrated a 6-year overall survival of 97% when the early carcinoma of the ovary prognostic score was below the cutoff value of 5.4, compared to 54% in patients with a higher score. Schueler et al also attempted to define alternative prognostic factors for early-stage ovarian cancer.[36] A total of 94 patients with FIGO stage I-IIA were divided into a well-differentiated group (group A, n = 64) and a moderately/poorly differentiated group (group B, n = 30). The prognostic significance of histologic grade, morphometric analysis, and DNA flow cytometry was evaluated. A significant difference in the 5-year, disease-free survival was found between groups A and B-91% and 75%, respectively. When the patients were grouped together, DNA index, histologic grade, and DNA ploidy were significant prognostic factors for disease-free survival. A DNA index of 1.40 was used to discriminate between low (< 1.40) and high aneuploid stromalines. Unlike the previous study, however, morphometric measurements did not add prognostic information.

- **Genetic Markers**- Other potential markers, such as altered expression of oncogenes and tumor-suppressor genes, have been studied as possible prognostic factors for ovarian cancer. Mutation of TP53 (alias p53) has been studied as a negative prognostic factor for early-stage ovarian cancer. Early results[37] did not show a correlation between p53 overexpression and adverse outcome; however, more recent results have demonstrated such a correlation. Unfortunately, many of these studies have relied on immunohistochemical analyses, which may not be completely accurate in all cases. Recently, the p53 mutation has been shown to be an adverse prognostic factor in a series of comprehensively staged early epithelial ovarian cancer patients.[38] In this series, p53 mutations were identified by sequencing and were associated with significantly worse progression-free and disease-specific survival rates.

- **VEGF Expression**- Vascular endothelial growth factor (VEGF) is a glycoprotein that stimulates angiogenesis. In a study of 68 patients with FIGO stage I/II ovarian cancers, Paley et al assessed the expression of VEGF and correlated it to outcome.[39] The tumor samples
of 29 patients showed overexpression of VEGF. The median survival in this group was 22 months, compared to more than 108 months in patients who did not express VEGF. After excluding the 13 patients with borderline tumors, the median survival rates for the VEGF-positive and -negative groups were 18 and more than 120 months, respectively. Other clinicopathologic factors such as tumor grade, FIGO stage, tumor size, and age had no significant impact on survival. VEGF overexpression was the strongest independent predictor of a poorer prognosis. Studies such as these may provide insight into additional prognostic factors that can help guide the treatment of early-stage tumors.

**Postoperative Treatment** Multiple factors must be considered when deciding on the use of adjuvant therapy in patients with early-stage ovarian cancer. As previously mentioned, two groups of patients with early-stage disease have been identified—low-risk and high-risk—based on clinicopathologic prognostic factors. **Low Risk**

- **Observation vs Adjuvant Therapy**- The prospective management of early-stage ovarian cancer patients with surgery alone has been reported. The GOG conducted a randomized trial of adjuvant therapy in comprehensively staged patients with stage I disease.[27] Eligible patients had FIGO stage IA/B tumors that were well or moderately differentiated. Patients were randomized to either observation or adjuvant treatment with melphalan (Alkeran). After a median follow-up of more than 6 years, no significant differences emerged between the two groups. The 5-year disease-free survival was 91% vs 98% (P = .41), and overall survival was 94% vs 98% (P = .43) in the observation and melphalan group, respectively. Of 8 patients with a clearcell histology, 3 (38%) relapsed, as compared to only 2 (3%) of 63 patients with other histologic types. This led the authors to recognize a low-risk group that included patients with disease confined to one or both ovaries, intact capsule, no adhesions or extracystic tumor, no ascites, negative peritoneal washings, and well- or moderately differentiated histologies. These patients had a good 5-year prognosis and did not seem to benefit from adjuvant therapy.

- **Well-Differentiated Tumors**- Trimbos et al reported the experience of a multicenter Dutch trial in patients with stage IA-IIA, well-differentiated ovarian cancer after primary surgery alone.[40] They identified 107 patients from nine Dutch oncology centers with early-stage, well-differentiated tumors. After further review, 21 patients were excluded for having second primary tumors (n = 7), adjuvant therapy (n = 2), wrong histologic grade (n = 10), wrong stage (n = 1), and surgery prior to the inclusion date (n = 1). Pathologic review demonstrated that 19 patients did not qualify; thus, the remaining 67 patients constituted the study population. Twenty-four patients had undergone comprehensive surgical staging, whereas 43 did not meet the surgical criteria. The 5-year disease-free survival rates were 100% and 88% in the comprehensively staged and incompletely staged groups. This demonstrated the good outcome among comprehensively staged patients with well-differentiated tumors.
Additional trials have prospectively treated early-stage epithelial ovarian cancer patients with surgery alone.[23,24,26,41] Survival rates have ranged from 83% to 98%. These series did not consistently include comprehensively staged patients, which may account for the variation in survival. It appears that patients with disease limited to the ovaries, who have well-differentiated tumors, have high enough survival rates that they do not benefit from adjuvant therapy. The treatment recommendation for patients with stage IA/B, grade 2 disease remains controversial, with some authors recommending adjuvant therapy[33] while others do not.[18] The importance of comprehensive staging prior to withholding adjuvant therapy cannot be stressed enough given that as many as 31% of patients will have subclinical metastasis that should be treated.[9]

**High Risk**
The role of chemotherapy in the management of advanced epithelial ovarian cancer is well documented. Even with a gross clinical resection of advanced disease, surgery alone is not curative. However, given the chemosensitive nature of these tumors, long-term survival can be achieved with the combination of chemotherapy and surgery. It remains to be determined whether adjuvant treatment is superior to no immediate treatment in patients with early-stage disease who are at risk for recurrence.
ACTION Trial-The European Organization for Research and Treatment of Cancer recently published the results of their Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial.[46] Patients were accrued from 40 centers in 9 European countries. Eligibility criteria included FIGO stage IA/B (grade 2/3)-IIA tumors or stage I-IIA clear-cell carcinomas in patients who had undergone surgical treatment consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy (in most cases), in addition to surgical staging. At a minimum, surgical staging involved careful inspection of the peritoneal surfaces, with biopsy of any suspicious lesion. Four classifications ranged from optimal (if a comprehensive staging procedure as previously described was performed) to inadequate (if peritoneal surfaces were inspected). Following surgery, 448 patients were randomized to either adjuvant platinum-based chemotherapy or observation, with the end points being overall survival and recurrence-free survival. The overall survival was similar in the two groups, with a hazard ratio of 1.45 (confidence interval [CI] = 0.93-2.27, \( P = .10 \)). Recurrence-free survival was improved in the adjuvant therapy group, with a hazard ratio of 1.59 (CI = 1.09-2.31, \( P = .02 \)). Because comprehensive staging was not mandated, only approximately one-third of patients qualified as being optimally staged. When the patients were analyzed based on the thoroughness of their staging, those who had not been optimally staged had improved disease-free and overall survival rates if they received adjuvant chemotherapy. However, no difference was identified among the optimally staged patients. The authors concluded that adjuvant chemotherapy was associated with improved recurrence-free survival. However, the benefits of chemotherapy appear limited to patients who do not undergo optimal staging and, thus, are at risk for having subclinical disease.

ICON1 Trial-Over a similar period as that of the ACTION trial, the International Collaborative Ovarian Neoplasm Collaborators (ICON) group conducted their own adjuvant chemotherapy trial in patients with early-stage ovarian cancer (ICON1).[47] Eligibility criteria were not as stringent for this trial in that entry was based on the clinician’s judgment and resulted in the inclusion of some occult advanced-stage patients. If the clinician was uncertain about the patient’s need for adjuvant chemotherapy, the woman was nonetheless eligible for the ICON1 trial, as long as all visible disease was removed. Hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were the minimum surgical requirements, and patients were randomized to a platinum-containing regimen or observation. With a median follow-up of 51 months, 5-year overall survival was 79% in the adjuvant therapy group, which was significantly better than the 70% rate in the observation arm. Disease-free survival was also significantly better in the adjuvant arm (73% vs 62%). The authors concluded that platinum-based adjuvant therapy improves survival and delays recurrence in patients with early-stage epithelial ovarian cancer.

Combined Analysis-In a preplanned combined analysis of the ACTION and ICON1 trials, the authors published the results for all 925 patients.[48] With a median follow-up of over 4 years, the 5-year overall survival was 82% in the chemotherapy arm and 74% in the observation arm (\( P = .008 \)). Recurrence-free survival at 5 years was also improved in the chemotherapy arm compared to the observation arm (76% vs 65%, \( P = .001 \)). However, because the majority of patients in this joint study were not optimally staged, the argument remains as to whether the presence of unappreciated residual disease could account for the apparent beneficial effect of adjuvant chemotherapy. Although platinum-based adjuvant therapy appears to have a role in the incompletely staged population, its role in comprehensively staged patients with early disease remains unanswered by this trial.[48]

GOG Study-The GOG recently reported the results of a randomized trial of adjuvant treatment in early-stage ovarian cancer patients with a poor prognosis. The object of this study was to determine whether an additional three cycles of chemotherapy (six cycles) would significantly lower the cancer recurrence rate. They compared adjuvant therapy with six cycles of paclitaxel (175 mg/m² over 3 hours) and carboplatin (AUC of 7.5 over 30 minutes) to the standard arm of three cycles of the same therapy.[49] All patients were required to have undergone a comprehensive staging laparotomy including retroperitoneal lymph node sampling. Of the 457 accrued patients, 107 were deemed ineligible due to incomplete staging. Of the 321 eligible patients, 241 (75%) were alive without recurrence at a median follow-up of 4.5 years. The risk of recurrence was 33% lower for patients treated with six cycles of chemotherapy (27% in the threecycle arm vs 19% in the six-cycle arm); however, this number did not reach statistical significance. When the analysis included incompletely staged patients, the recurrence rate was 24% lower (not statistically significant).
in the six-cycle arm, but toxicity was significantly greater. The authors concluded that the additional three cycles of carboplatin and paclitaxel did not significantly improve the recurrence rate in these early-stage patients, but it did result in more toxicity.

**Intraperitoneal Chemotherapy**

Other forms of adjuvant therapy have been studied in the management of early-stage ovarian cancer. Direct application of chemotherapy into the peritoneal cavity has been studied because, in the majority of cases, this disease remains confined to the peritoneal cavity. Malmstrom et al used intraperitoneal carboplatin as adjuvant therapy for early-stage ovarian cancer patients.[50,51] In a phase I study, they demonstrated that intraperitoneal carboplatin, which has a peak peritoneal cavity/peak plasma concentration ratio of 18, can be given at a maximum tolerated dose of 500 mg/m².[50] The same group followed this study with a phase II trial in 47 patients (31 FIGO stage I and 16 stage II) with early-stage ovarian cancer who were treated with four cycles of intraperitoneal carboplatin.[51] Recurrent disease was documented in 10 patients (23%), and the median time to recurrence had not been reached among the 43 evaluable patients after a median follow-up of 26.2 months. The authors concluded that intraperitoneal carboplatin demonstrated moderate activity with acceptable toxicity as adjuvant chemotherapy for early-stage ovarian cancer. The advantages of intraperitoneal vs intravenous therapy for early-stage ovarian cancer have yet to be proven.

**Radiation Therapy External-Beam Irradiation**

Two methods have been used to incorporate radiation therapy into the management of early-stage ovarian cancer. External-beam irradiation has been evaluated as adjuvant therapy in patients with early-stage disease. Several trials have also included optimally debulked patients with advanced disease, and this must be kept in mind when interpreting these studies. Because ovarian cancer tends to disseminate throughout the entire peritoneal cavity, adjuvant external-beam radiation therapy should be directed to encompass both the abdomen and pelvis. Two prospective randomized trials have compared the role of pelvic irradiation to observation. A GOG study randomized 168 stage I patients to observation, pelvic radiation, or melphalan.[52] Of the entire group, only 86 were eligible for analysis; thus, the treatment arms were not equally matched for prognostic variables. Neither pelvic irradiation nor melphalan reduced the recurrence rate when compared to observation. Similar results were reported by Dembo et al, who randomized 41 stage IA patients to pelvic radiation therapy or observation.[53] Four relapses occurred in the radiation arm and one in the observation arm. The authors concluded that no benefit in survival or prevention of relapse was associated with pelvic irradiation because the entire peritoneal cavity was at risk for failure. **Whole Abdominal Radiation**

The lack of effective control with pelvic radiation therapy led to studies of whole abdominal radiation. Several randomized trials comparing whole abdominal radiation to chemotherapy as adjuvant treatment for early-stage ovarian cancer have been reported in the literature (Table 8).[54-58] Of these, only one demonstrated a significant benefit. Dembo et al reported their experience with 147 patients with stage I-III ovarian cancer.[58] Patients received either abdominopelvic or pelvic irradiation, with or without chlorambucil (Leukeran). The benefit was seen only in patients in the abdominopelvic radiation arm with less than 2 cm or no residual disease; the 10-year survival of these patients was 64%, compared to 40% for patients in the pelvic radiation group (P = .0007). Patients with residual disease greater than 2 cm did not show any benefit.
In a randomized trial of whole abdominal radiation (2,600-2,800 cGy) with a 2,000-cGy pelvic boost vs melphalan (12 cycles of 0.2 mg/kg/d for 5 days), Smith et al reported a 2-year disease-free survival of 85% vs 90% among stage I patients treated with whole abdominal radiation and chemotherapy, respectively.[55] For stage II patients, the disease-free survival rates were 55% and 58%, respectively. No information on statistical significance was reported in this study. Klaassen et al evaluated 257 optimally debulked stage I-III ovarian cancer patients who were randomized to intraperitoneal P-32 (10-15 mCi), melphalan (8 mg/m²/d for 4 days every 4 weeks for 18 cycles), or whole abdominal radiation (2,250 cGy over 20 fractions using the moving-strip technique).[54] Comprehensive staging was not mandatory. All patients were initially treated with pelvic radiation (2,250 cGy before whole abdominal radiation or 4,500 cGy before melphalan or P-32). With a median follow-up of 8 years, 5-year disease-free survival rates were similar for the three arms at 66%, 61%, and 62%, but the authors also noted that protocol violations in the whole abdominal target volume were associated with reduced survival. Although earlier randomized trials have compared whole abdominal radiation to non-platinum-based chemotherapy regimens, the Northwest Oncologic Cooperative Group of Italy attempted to compare whole abdominal radiation (4,330 cGy/24 fractions of pelvic radiation plus 3,020 cGy to the upper abdomen) to six cycles of adjuvant cisplatin (50 mg/m²) and cyclophosphamide (Cytoxan, Neosar [600 mg/m²]) in patients with stage I/II disease.[57] The study was closed early due to poor protocol compliance and low accrual. With a median follow-up of 60 months, the 5-year survival was 71% and 53% (P = .16), and the relapse-free survival was 74% and 50% (P = .07) for the chemotherapy and whole abdominal radiation arms, respectively. When the data were analyzed according to treatment received rather than treatment assigned, no significant difference in relapse-free survival (73% vs 60%) or overall survival (73% vs 68%) was detected for patients receiving chemotherapy and whole abdominal radiation. The role of external-beam radiation as adjuvant therapy for early-stage ovarian cancer remains unclear. It is apparent that adjuvant radiation should encompass the entire abdomen because these patients are at risk for relapse in the entire peritoneal cavity. Although the older studies have demonstrated that whole abdominal radiation may be as effective as chemotherapy, these results have yet to be adequately demonstrated in patients with early-stage disease who have been treated with modern-day agents. The evolution of modern chemotherapy for ovarian cancer may make efforts to study adjuvant radiation therapy difficult.
Intraperitoneal Radioactive Isotopes

Radioactive isotopes have been used as adjuvant therapy for early-stage ovarian cancer, with P-32 being the most commonly used. P-32 is an emitter of beta radiation only, which avoids the toxicity associated with gamma radiation. It has a half-life of 14.3 days and an average tissue penetration of 1.4-3.0 mm. After it is instilled into the abdomen, the patient is placed in several positions to ensure adequate distribution throughout the peritoneal cavity. As one might suspect, distribution of the radioactive colloid may be a potential problem. The intraperitoneal distribution can be tested prior to P-32 instillation with radioactive technetium sulfur colloid or after radiocolloid instillation with scintigraphic imaging of Bremsstrahlung photons. Distribution patterns of intraperitoneal P-32 have been studied by Vergote et al.[59] They used a gamma camera to detect Bremsstrahlung photons in 297 patients. Images were obtained 2 to 24 hours and 3 to 7 days following administration of P-32, and they demonstrated an uneven distribution in 165 patients, loculation in 2%, leakage in 3%, and uptake in the thoracic lymph nodes in 54%. There was uneven accumulation of isotope in the pelvis (60%) and right flank (33%). The investigators found that 46% of patients initially had even P-32 distribution but later (at 3 to 7 days) had major accumulation. No relationship was noted between uneven distribution, loculation, or leakage of P-32 and relapse or bowel obstruction. Several studies have compared the use of intraperitoneal P-32 as adjuvant treatment for early-stage disease (Table 9).[27,44,52,54,60] As previously mentioned, the National Cancer Institute of Canada examined the use of intraperitoneal P-32 compared to whole abdominal radiation and melphalan in patients with high-risk stage I/II disease or optimally debulked stage III disease.[57] Comprehensive staging was not mandatory, and with a median follow-up of 8 years, 5-year survival rates were similar. The authors noted a high incidence of bowel complications in the P-32 and pelvic radiation arm, and this trial was closed prematurely.

GOG Studies-The GOG studied the use of adjuvant therapy in 141 patients with poorly differentiated stage I or stage II tumors.[27] Patients were randomly assigned to either 12 cycles of melphalan (0.2 mg/kg/d) for 5 days every 4 to 6 weeks or one dose (15 mCi) of intraperitoneal P-32 at the time of surgery. With a median followup of greater than 6 years, disease-free survival was 80% in both arms and overall survival was 81% and 78% with melphalan and P-32, respectively ($P = .48$). Twenty-four of the patients were reclassified as having borderline tumors, but they were evenly distributed between the two groups. Exclusion of these patients reduced the 5-year survival rate to 76%. When comparing the two treatment regimens, the GOG decided to label P-32 as the standard, given its lower cost, ease of administration, and lack of leukemic risk. The GOG subsequently compared adjuvant P-32 to three cycles of cyclophosphamide and cisplatin in patients with stage IC and II tumors and no macroscopic residual disease and patients with poorly differentiated stage IA/B tumors.[52] A total of 205 patients were randomized, and the median follow-up was 6 years. The 5-year recurrence-free survival rate was 77% for the chemotherapy arm and 66% for the P-32 arm. After adjusting for stage and histologic grade, the estimated recurrence rate was 31% lower in the chemotherapy arm; however, this was not statistically significant ($P = .075$). Overall, the 5-year survival rate was 84% for the chemotherapy arm and 76% for the

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**Table 9**

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease Stage</th>
<th>Number of Patients</th>
<th>Treatment</th>
<th>Outcome</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al., 1990[27]</td>
<td>IA/B (grade 3), stage II</td>
<td>26</td>
<td>Melphalan</td>
<td>80% (5-yr disease-free survival)</td>
<td>.87</td>
</tr>
<tr>
<td>Young et al., 1999[52]</td>
<td>IA/B (grade 3), stage II</td>
<td>107</td>
<td>Cisplatin/cyclophosphamide</td>
<td>P-32</td>
<td>.08</td>
</tr>
<tr>
<td>Vergote et al., 1992[80]</td>
<td>I, II, III optimally debulked</td>
<td>171</td>
<td>Cisplatin</td>
<td>75% (5-yr disease-free survival)</td>
<td>.57</td>
</tr>
<tr>
<td>Boz et al., 1995[44]</td>
<td>IC</td>
<td>82</td>
<td>Cisplatin</td>
<td>85% (5-yr disease-free survival)</td>
<td>.008</td>
</tr>
<tr>
<td>Klaassen et al., 1988[54]</td>
<td>IC-III optimally debulked</td>
<td>107</td>
<td>Whole abdominal radiation</td>
<td>62% (5-yr overall survival)</td>
<td>NS</td>
</tr>
</tbody>
</table>

P-32 arm.[52] Although no significant difference in survival emerged between the two arms, the better progression-free interval with the cyclophosphamide and cisplatin therapy, as well as the associated problems with P-32 distribution and bowel toxicities, made platinum-based combinations the standard adjuvant therapy for patients with early-stage, high-risk ovarian cancer.

- **Vergote et al Study** - Vergote et al[60] reported their experience with 347 patients with stage I-III epithelial ovarian cancer and no residual disease. Comprehensive staging was not required in this series. Patients were randomized to receive intraperitoneal P-32 (7-10 mCi) or six cycles of cisplatin (50 mg/m²). Patients randomized to the P-32 arm who were found to have intraperitoneal adhesions were treated with whole abdominal radiation. With a median follow-up of 62 months, the estimated 5-year rates of crude survival and disease-free survival were similar. In the P-32 arm, these were 83% and 81%, respectively, compared to 81% and 75% in the cisplatin arm. Bowel obstruction occurred with a significantly higher frequency in the P-32 or whole abdominal radiation groups compared to the cisplatin group. The authors recommended that cisplatin be used for adjuvant therapy in future studies.

- **GICOG Study** - As noted in the discussion of chemotherapy above, the Italian collaborative group, Gruppo Interregionale Collaborativo in Ginecologia Oncologica (GICOG), simultaneously reported on two randomized trials of adjuvant therapy (cisplatin vs observation, and cisplatin vs P-32) for early-stage ovarian cancer.[44] Again, no significant difference in 5-year overall survival emerged in either trial, which the authors suggested may be due to the limited impact of adjuvant therapy, low doses at which the cisplatin was administered, impact of salvage therapy, or because the study was underpowered (see chemotherapy section for details of these studies).

**Conclusions** Despite the high mortality generally associated with ovarian cancer, about one-third of patients present with curable disease. The importance of accurate surgical staging of patients with suspected early-stage ovarian cancer cannot be stressed enough. New approaches to comprehensive staging are beginning to appear and have been shown to be technically feasible. The validity of these approaches as acceptable alternatives to traditional staging via laparotomy remains to be established. Patients with disease confined to the ovary and certain favorable prognostic factors have been shown to achieve good outcomes with surgery alone. Several clinicopathologic prognostic factors have been shown to be associated with a poorer outcome, and newer factors have been linked to a poorer prognosis. In such cases, it is reasonable to use adjuvant therapy to try to improve survival. Modern dosing and premedication regimens have made chemotherapy very tolerable and the preferred form of adjuvant therapy for these early-stage patients.

**Disclosures:**
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**
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