Advances in the Treatment of Gynecologic Malignancies

Over the past few decades, we have gained a better understanding of the risk factors associated with the recurrence of endometrial cancer. Adjuvant postoperative radiotherapy in an intermediate-risk group of patients was discussed in part 1 of this article, which appeared in last month's issue of ONCOLOGY, summarized the outcome of major phase III trials in cervical and vulvar cancer. This part will provide the outcome of phase III trials in uterine and ovarian cancer.

Early-Stage Endometrial Cancer

Endometrial cancer is the most common female genital tract cancer in the United States. The majority of cases are confined to the uterus. Treatment of organ-confined uterine cancer usually comprises total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO). In 1988, clinical staging of endometrial cancer was replaced with surgical staging because of inaccuracies associated with clinical staging. Over the past several decades, we have learned more about the risk factors associated with the recurrence of endometrial cancer. In recent years, few prospective phase III randomized studies have been conducted in patients with endometrial carcinoma to answer questions regarding the best management of these patients.

Surgical/Pathologic Study

**GOG-33** This Gynecologic Oncology Group (GOG) study conducted by Creasman et al enrolled 621 patients with stage I/II cancer of the endometrium. All patients underwent TAH/BSO, selective pelvic and para-aortic lymphadenectomy, and peritoneal cytology. The depth of myometrial invasion and grade of tumor were the most important factors predicting pelvic node and para-aortic node metastases (Table 1).

Before 1988, endometrial cancer was clinically staged. However, Creasman et al showed that, when a comprehensive staging procedure is performed, 22% of clinical stage I patients have disease outside the uterus. As a result, the International Federation of Gynecology and Obstetrics (FIGO) mandated that this disease be staged surgically.

The requirement for lymph node assessment has been the subject of considerable debate. To different practitioners, this assessment may imply observation, palpation, sampling, or dissection. GOG findings confirmed that fewer than 10% of patients with nodal metastases have grossly positive nodes. Therefore, visualization and palpation are inadequate to exclude lymph node involvement. Pelvic lymph node dissection should be performed via multiple-sites because retrospective evidence indicates that adequate pelvic lymph node dissection may improve overall survival.

**Risk Groups** In general, patients can be divided into one of three categories of risk for developing recurrent and metastatic disease: low risk, intermediate risk, and high risk. When the patient's tumor is confined to the uterus, the primary risk factors are tumor grade, tumor histology, and depth of invasion. Depending on the individual patient risk factors, organ-confined endometrial cancer can be classified as either low risk (grade 1/2, endometrial invasion only, excluding clear cell and papillary serous cases) or intermediate risk (grade 1-3, inner/middle myometrial invasion). Patients at high risk have cervical involvement and tumor spread beyond the uterus.

Radiation is often administered to women at risk for extraterine spread when the status of the lymph nodes is unknown. However, the adoption of surgical staging has led to questions regarding the role of pelvic radiotherapy in patients with disease confined to the uterus.
Adjuvant Treatment of Organ-Confined Disease

• **GOG-99**—Roberts et al evaluated surgery vs surgery plus adjuvant radiotherapy in patients with intermediate-risk (stage IB, IC, and occult stage II) endometrial cancer; clear cell and serous carcinomas were excluded.[4] All patients underwent complete surgical staging with pelvic and para-aortic lymph node dissection and peritoneal cytology. Patients with intermediate-risk, surgical stage I disease were then randomized to either no further therapy or 50.4-Gy pelvic irradiation. A preliminary report of this study showed that the pelvic recurrence rate was 12% without radiotherapy vs 1.7% with radiotherapy. Two-thirds of the pelvic recurrences were in the vagina alone (15/22, 68% of all recurrences in the surgery-alone arm, as well as the only failure among patients receiving radiation). Although the disease-free survival rate significantly favored the radiotherapy arm—93.7% vs 84.7%, respectively ($P = .04$)—there was no significant difference in the overall survival rate at 3 years (89% vs 96%, $P = .09$). This study will require further follow-up before a final analysis of overall survival can be performed.

The intermediate-risk group represents a heterogeneous group of patients. The patient population accrued in this study was much more favorable than anticipated (< 18% had outer one-third myometrial invasion, and 81.6% had grade 1 and 2 tumors), leaving the study insufficiently powered to observe survival differences. Therefore, the role of pelvic irradiation in patients with deep myometrial invasion and high-grade tumor is still unclear and needs to be studied further.

Since the main benefit of pelvic irradiation is a decrease in the vaginal recurrence rate, it could be argued that women with intermediate-risk tumors, especially those who are well staged, should receive adjunctive vaginal vault radiation therapy only, which has fewer side effects. Several retrospective studies have demonstrated excellent outcomes with this approach.[5-8] Because of increased vaginal sequelae, treatment of the entire length of the vagina is usually not recommended.

• **NCIC trial**—An ongoing trial being conducted by the National Cancer Institute of Canada (NCIC) clinical trial group is similar to GOG-99. The accrual goal is approximately 400 patients. The results of this study will help clinicians make appropriate therapeutic decisions for this patient population.

• **RTOG-99-05**—Recently, the Radiation Therapy Oncology Group (RTOG) initiated a phase III study (99-05) of adjuvant postoperative irradiation with or without cisplatin and paclitaxel following TAH/BSO in patients with endometrial cancer. Selection criteria include uterine-confined cancer, but this population (with stage IC and IIA/B disease) is at higher risk of disease recurrence than were women enrolled in GOG-99. Regional lymph node sampling is not necessary for this study population.

• **Other Trials in Organ-Confined Disease**—Table 2 compares the parameters of GOG-99 with those in two other randomized trials of clinically organ-confined endometrial cancer.[4,9,10] In 1980, Aalders et al[9] published a report on a randomized trial of primary surgery and vaginal brachytherapy with and without additional external-beam radiation in patients with endometrial cancer. As expected, a significant reduction in vaginal and pelvic recurrences was observed in the group receiving adjuvant radiotherapy (1.9% vs 6.9%). However, the overall 5-year survival did not improve. In subset analysis, those with grade 3 lesions and > 50% myometrial invasion showed a significant increase in survival. Pelvic node dissection was not performed in this study.

In most European countries, lymphadenectomy is not considered a standard procedure for stage I endometrial cancer. Recently, the Dutch Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) study group[10] investigated whether postoperative pelvic irradiation improved locoregional control and survival in patients with stage I endometrial cancer. The 715 patients in the intermediate-risk group were randomized to pelvic radiotherapy (46 Gy) or no further treatment, and pelvic node dissection was not performed. The 5-year locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group, but there was no impact on overall survival. The majority of recurrences (73%) were restricted to the vagina. As expected, the incidence of late complications was higher in the radiotherapy group (25% vs 6%), although most were grade 1.
The results of both the Aalders and PORTEC trials[9,10] are based on clinically staged patients and may not be relevant for surgically staged patients. Another Dutch trial in which lymphadenectomy is being compared to radiotherapy in high-risk endometrial cancer has recently been initiated, and the results of that trial will clarify the future role of lymphadenectomy in endometrial cancer.

**Advanced-Stage Endometrial Cancer**

Treatment of advanced-stage (high-risk) endometrial cancer remains problematic. Various investigators have observed that patients with extraterine spread limited to the peritoneal fluid and/or adnexa (stage IIIA) have favorable outcomes compared with patients with nodal or other intra-abdominal metastasis. Predominantly, pelvic or abdominal irradiation has been used as adjuvant therapy for these stage IIIA patients. A previous phase II GOG trial established whole-abdominal irradiation in maximally debulked advanced disease to be tolerable and reasonably efficacious. Survival at 3 years for patients with surgically staged III and IV disease was 31% for typical adenocarcinoma and 33% for papillary serous and clear cell carcinoma.[11]

In previous GOG trials,[12,13] doxorubicin, cisplatin, and paclitaxel have shown single-agent activity in patients with measurable, advanced endometrial cancer. Despite the excellent response rate, time to disease progression and median survival for most patients has generally ranged from 4 to 10 months.

- **GOG-34**—Morrow et al attempted to evaluate the effect of doxorubicin after involved-field local radiotherapy for locally advanced endometrial cancer.[14] The study population consisted of patients with clinical stage I or II (occult) disease who had one or more risk factors for recurrence (greater than 50% myometrial invasion, pelvic or aortic node metastasis, cervical involvement, or adnexal metastases). All patients received involved-field irradiation (45-50 Gy). After completion of radiotherapy, patients were randomized to receive doxorubicin (at a starting dose of 60 mg/m², every 3 weeks) to a maximum cumulative dose of 500 mg/m², or no further treatment. There was no statistically significant difference in survival or progression-free interval between the two groups. Because of protocol violations, small sample size (90 patients in each arm), and the number of patients lost to follow-up, the study was unable to determine what effect the use of doxorubicin as adjuvant therapy had on recurrence, progression, and survival.

- **GOG-122**—This study compared whole-abdominal irradiation vs doxorubicin and cisplatin in 390 patients with surgical stage III/IV disease and ≤ 2.0 cm residual disease of any histology, including clear cell and serous papillary carcinoma. The study was closed in February 2000, and the results are pending.

- **GOG-184**—With the same patient population as GOG-122, this two-arm study is investigating whether any further advantage may be realized by combining both adjuvant modalities. Patients receive postoperative pelvic irradiation to a total dose of 50.4 Gy; if the para-aortic nodes are pathologically positive, patients also receive 45 Gy of pelvic para-aortic irradiation. After irradiation is completed, patients are randomized to one of two chemotherapy regimens for six cycles, administered at 3-week intervals: doxorubicin (45 mg/m²) plus cisplatin (50 mg/m²), or doxorubicin (45 mg/m²), cisplatin (50 mg/m²), paclitaxel (160 mg/m²), and granulocyte colony-stimulating factor (G-CSF [Neupogen], 5 µg/kg on days 3-12).

**Uterine Sarcomas**

Carcinosarcomas and other uterine sarcomas are uncommon tumors, accounting for less than 4% of all cancers of the uterine corpus. The most common histologic subtype, carcinosarcomas (malignant mixed mesodermal tumor) demonstrate both epithelial and stromal differentiation. Endometrial stromal sarcomas and leiomyosarcomas are characterized by differentiation toward one or more stromal tissues.

Surgery is the mainstay of treatment for uterine sarcomas. Currently, no clear data have suggested
improvement in outcome for these patients following treatment with adjuvant pelvic radiation or systemic chemotherapy. Ifosfamide (Ifex) appears to be the most active agent for carcinosarcoma,[15] whereas doxorubicin is most active in leiomyosarcoma.[16] Responses to progestins have been reported in advanced or recurrent stromal sarcoma.[17] A response to the aromatase inhibitor letrozole (Femara), which blocks the enzyme responsible for estrogen biosynthesis, was recently demonstrated.[18]

• **GOG-20** Omura et al conducted a randomized study of prophylactic doxorubicin for 6 months vs no adjuvant chemotherapy in 156 patients with stage I/II uterine sarcoma. Pelvic irradiation was optional before randomization.[19] The investigators reported no difference in progression-free interval or survival. The optional radiotherapy did not influence outcome, although there was a suggestion that the incidence of vaginal recurrences was decreased by pelvic irradiation.

The recurrence rates in specific cell types were not significantly different, although the pattern of recurrence differed, with pulmonary metastases being more common in leiomyosarcomas and abdominal recurrence more common in carcinosarcoma. Therefore, the GOG is studying whole-abdominal radiotherapy in carcinosarcoma. The current protocol (GOG-150) is a phase III randomized study of whole-abdominal irradiation vs the combination of ifosfamide (Ifex)/mesna (Mesnex) with cisplatin in optimally debulked stage I-IV carcinosarcoma of the uterus.

**Early-Stage Ovarian Cancer**

Approximately 20% to 25% of patients with ovarian cancer have early-stage disease (stage I/II) at the time of diagnosis. The published 5-year survival rates range from 50% to 70% for stage I disease and 40% to 60% for stage II disease.[20,21] Prognostic factors such as cell type and histologic grade provide only a partial explanation for these widely variable results. Earlier studies demonstrated the need for thorough surgical staging to define the extent of disease and for a prospective comparison of treatments in groups of patients balanced for known prognostic factors.

**Surgical/Pathologic Studies**

• **GOG-41** Buchsbaum et al conducted a surgical-staging study in 187 ovarian cancer patients with stage I-III optimal epithelial carcinoma of the ovaries.[22] Results demonstrated the poor correlation between clinical assessment by palpation and histologic examination: For the omentum, the clinical impression was inaccurate in 45%; for the diaphragm, the clinical impression was negative in half of patients with a positive biopsy; in the case of pelvic nodes, the clinical impression was negative in 71% with positive nodes; for para-aortic nodes, the clinically false-negative figure was 96%.

The study indicated that surgical exploration for early-stage cancer of the ovary should include biopsy of retroperitoneal pelvic and para-aortic lymph nodes, excision of the infracolic omentum, biopsies of the pelvic and abdominal peritoneum including the right diaphragm, and peritoneal cytologic studies.

**Adjuvant Radiotherapy vs Chemotherapy**

Surgery plays a crucial role in all phases of the management of ovarian cancer. However, surgery is frequently not curative due to dissemination of tumor cells throughout the abdominal cavity. Therefore, successful management generally requires additional treatment. Table 3 summarizes the series of GOG studies of adjuvant radiotherapy in this setting.[23-25]

• **Early GOG Studies** The first GOG trial (GOG-1)[23] dealt with early ovarian cancer comparing observation, pelvic irradiation, and melphalan (Alkeran), and showed less recurrence with melphalan but no survival differences. All patients, with the possible exception of those with stage IA/B, grade 1/2 disease, appeared to benefit from adjuvant chemotherapy compared to no treatment or radiotherapy.

The next trial,[24] which was conducted in conjunction with the Ovarian Cancer Study Group (OCSG), required carefully predefined surgical staging. Patients with stage IA/B disease and
well-differentiated or moderately differentiated grades were randomized to observation vs melphalan chemotherapy. The 5-year survival rate exceeded 90% in both arms, and the conclusion was that this favorable group did not require any postoperative adjuvant therapy. Patients with poorly differentiated stage I disease and all patients with stage II disease were randomly assigned to treatment with either melphalan or a single intraperitoneal dose of phosphorus (P)-32 (15 mCi) at the time of surgery. However, the outcome for both treatments was similar with respect to 5-year disease-free survival (80% in both arms).

The next GOG trial (GOG-95)[25] compared intraperitoneal P-32 with the combination of cisplatin and cyclophosphamide (Cytoxan, Neosar) in 205 patients with high-risk, early-stage ovarian cancer. Although no difference in overall survival was observed, platinum-based chemotherapy was associated with a 31% reduction in risk of recurrence compared with intraperitoneal P-32. With a median follow-up of 6 years, the investigators found a borderline impact (P = .075) on progression-free survival for the chemotherapy regimen (84% vs 76%). Although not statistically significant differences, the better progression-free interval with chemotherapy and the bowel toxicities associated with P-32 favored platinum-based therapy as a control arm in further GOG studies of early-stage, high-risk ovarian cancer.

• **Italian Inter-Regional Cooperative Group Studies**[26] The Italian Inter-Regional Cooperative Group[26] conducted two randomized trials to evaluate the role of adjuvant therapy in patients with stage I ovarian cancer. The first compared cisplatin to observation in 85 patients with stage IA/B, grade 2/3 disease. The 5-year disease-free survival rate was higher among patients receiving cisplatin (83% vs 63%), but 5-year overall survival was similar in the two groups (88% vs 83%). The second trial compared cisplatin to P-32 in 161 patients with stage IA2, IB2, and IC disease. The 5-year disease-free survival rate again favored the cisplatin arm (85% vs 65%), but 5-year overall survival was similar.

• **GOG-157/GOG-175**[25] Based on the results of recent chemotherapy studies in advanced ovarian cancer, the combination of paclitaxel with platinum agents is currently considered one of the more promising adjuvant chemotherapy regimens. Therefore, the next two GOG trials in high-risk early-stage ovarian cancer investigated paclitaxel and carboplatin (Paraplatin) as adjuvant chemotherapy. GOG-157 randomized patients to three or six cycles of adjuvant paclitaxel plus carboplatin. GOG-175 is an ongoing phase III trial in which patients receive three cycles of paclitaxel/carboplatin and then are randomized to weekly paclitaxel for 24 weeks or observation. The results of both studies are pending.

• **ICON-1/ACTION**[27] In the meantime, preliminary results of a large European study, the so-called International Collaboration on Ovarian Neoplasm/Adjuvant Treatment in Ovarian Neoplasm (ICON-1/ACTION) trial,[27] were presented. A total of 923 patients were randomized to platinum-based chemotherapy or observation. Disease-free survival was significantly different, but overall survival only differed significantly when data from ICON-1 and ACTION were combined. In optimally staged patients, no survival advantage was associated with adjuvant therapy.

**Advanced-Stage Ovarian Cancer**

The management of ovarian cancer has advanced notably during the 1990s, but remains a challenge because diagnosis of early-stage disease is the exception, not the rule. Today, 75% of patients with advanced ovarian cancer can expect to achieve remission following primary cytoreductive surgery and systemic chemotherapy. Unfortunately, the initial benefit of surgery and chemotherapy is usually not durable; the median time to progression is 18 to 24 months.

**Emergence of Platinum-Based Combination Chemotherapy**

The ovarian cancer mortality rate remained relatively unchanged from the 1950s to the 1970s, despite advances in surgical and radiologic approaches. Whole-abdominal irradiation has several theoretical and practical advantages over P-32 therapy, including better coverage of all peritoneal surfaces with improved homogeneity of radiation dose, and lack of treatment restrictions due to postoperative adhesions. The first randomized radiotherapeutic trial (GOG-2)[28] compared
whole-abdominal irradiation vs melphalan vs whole-abdominal irradiation plus melphalan. However, no difference in survival was observed.

It became increasingly apparent that the advanced nature of the vast majority of ovarian cancers necessitated systemic chemotherapy. Single-alkylating-agent therapy (usually melphalan) was the standard of care until the mid-1970s. The next step in the search for effective chemotherapeutic regimens was the development of combination drug therapies.

- **GOG-22** This trial compared melphalan vs melphalan plus altretamine (Hexalen) vs cyclophosphamide plus doxorubicin in bulky stage III/IV cases. After adjusting for cell type and grade of differentiation, cyclophosphamide plus doxorubicin produced a significantly higher clinical complete response rate than melphalan alone (32% vs 20%). Melphalan plus altretamine was not significantly better than melphalan alone, and neither combination improved response duration or survival compared with melphalan alone.

- **GOG-47** In view of the improvement in response rate with cyclophosphamide plus doxorubicin, the combination was chosen for further study. In the 1970s, a breakthrough occurred in the chemotherapeutic management of ovarian cancer when cisplatin was introduced into the clinic. Thus, the use of cyclophosphamide plus doxorubicin, with or without cisplatin, was evaluated in GOG-47.

CAP (cyclophosphamide, doxorubicin [Adriamycin], cisplatin [Platinol]) produced a statistically significant improvement in clinical complete response rate (51% vs 26%), response duration (14.6 vs 8.8 months), and progression-free interval (13.1 vs 7.7 months) compared with CA (cyclophosphamide, doxorubicin; Table 4). A statistically significant survival advantage was demonstrated for CAP in patients with measurable disease. In fact, this benefit was seen in both measurable and nonmeasurable cases after adjusting for important prognostic factors.

- **GOG-52** Investigators remained concerned about the value of the other agents in CAP, especially doxorubicin, as other studies had failed to show a major advantage with their addition to treatment regimens. GOG-52 compared CAP vs the combination of cyclophosphamide and cisplatin, at doses with comparable hematologic toxicity. The study again failed to demonstrate an advantage for the inclusion of doxorubicin. As a result, the use of doxorubicin in primary therapy declined, especially in the United States. Subsequently, a meta-analysis revealed a small but significant improvement in outcome for the inclusion of doxorubicin. Interest in anthracyclines as part of first-line therapy has continued in Europe.

**Emergence of the Taxanes**

Substantial cross-resistance between platinum compounds and other active agents (particularly alkylating agents and anthracyclines) remained an obstacle to improving long-term outcomes and emphasized the need for agents with new mechanisms of action. In the 1980s, paclitaxel underwent phase II evaluation for ovarian cancer and demonstrated response rates greater than 20%, even in platinum-refractory patients. The activity of paclitaxel in platinum-refractory ovarian cancer coupled with the poor long-term outcome of standard therapy led to rapid phase III evaluation of its role as a component of platinum-based combination chemotherapy (Table 5).

- **GOG-111** The GOG initiated the first phase III study designed to compare cisplatin/paclitaxel with the standard first-line regimen of cisplatin/cyclophosphamide in patients with large-volume ovarian cancer. The results of this landmark study showed that the paclitaxel-containing regimen was more favorable in terms of the following four parameters: response to therapy (73% vs 60%, \(P = .01\)), clinical complete response rate (51% vs 31%, \(P = .01\)), median progression-free survival (18 vs 13 months, \(P < .001\)), and overall survival (36 vs 24 months, \(P < .001\)). The impact of this finding was as great as that of GOG-47 on cisplatin-based combination therapy.

- **OV-10** A European-Canadian collaborative group (OV-10) sought to confirm the activity of cisplatin/paclitaxel in advanced ovarian cancer. This study differed from GOG-111 in that patients
with small-volume disease were eligible to participate. Paclitaxel at 175 mg/m² was administered over 3 hours (as compared with 135 mg/m² over 24 hours in GOG-111). Outcome in this study essentially replicated the progression-free and overall survival rates of GOG-111.

- **GOG-132** - Before the results of GOG-111 were available, the GOG initiated another randomized study in a similar patient population with large-volume ovarian cancer (GOG-132).[38] Eligible patients were randomized to receive one of the following regimens: cisplatin/paclitaxel as in GOG-111, single-agent cisplatin (100 mg/m²), or single-agent paclitaxel (200 mg/m²). After a median follow-up of 61 months, overall survival duration was similar among the treatment groups (30.2, 25.9, and 26.3 months, respectively, \( P = .310 \)). Although the higher doses of cisplatin and paclitaxel in the single-agent arms could have influenced the result, the crossover of many patients in the single-agent arms to the other agent is of greater concern. Crossover may have obscured potential survival differences in this study and led to an unintentional comparison of concurrent vs sequential chemotherapy. Based on the favorable safety profile of cisplatin/paclitaxel and the survival benefits demonstrated in both GOG-111 and OV-10, GOG investigators concluded that the combination of cisplatin/paclitaxel should remain the standard of care.

**Carboplatin/Paclitaxel vs Cisplatin/Paclitaxel**

In an effort to reduce the toxicity of therapy for advanced ovarian cancer and develop a regimen that can be easily administered in the outpatient setting, investigators have explored the combination of carboplatin/paclitaxel. Two large randomized trials comparing this combination to a regimen of cisplatin plus paclitaxel established that carboplatin/paclitaxel had a better therapeutic index (Table 6).[39,40]

- **GOG-158** - This trial compared carboplatin/paclitaxel to a control regimen of cisplatin/paclitaxel in patients with small-volume residual stage III ovarian cancer.[39] There was no difference in overall survival between the treatment arms. Although not a stated objective of the protocol, the potential benefit of a second-look procedure was also investigated in this study; assignment to this course of action was not randomized, but rather, was selected by the surgeon before treatment began. Second-look surgery had no impact on progression-free survival in these patients, who initially had optimally debulked disease.

- **AGO Study** - The German Arbeitsgemeinschaft Gynekologische Onkologie (AGO) study group[40] confirmed the results of GOG-158 in 798 patients with advanced ovarian cancer. The carboplatin-based regimen was shown to be significantly less toxic (specifically, in terms of emesis and neurotoxicity) than cisplatin plus paclitaxel.

Several new agents (topotecan [Hycamtin], gemcitabine [Gemzar], liposomal doxorubicin [Doxil]) have been found to be active in ovarian cancer. How to integrate them into first-line therapy and whether they will improve outcome remains to be determined, and is the subject of a current international trial.

**Docetaxel/Carboplatin vs Paclitaxel/Carboplatin**

A preliminary report of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC), which is comparing DC (docetaxel [Taxotere], carboplatin) vs PC (paclitaxel/carboplatin), showed no difference in outcome.[41] Patients receiving DC had more neutropenia but less neuropathy. Publication of this trial is awaited with interest.

**Intraperitoneal Chemotherapy**

In an attempt to maximize its activity against ovarian cancer, cisplatin has been administered directly into the peritoneal cavity in investigational studies. This route yields an intraperitoneal concentration of cisplatin that is 12 to 15 times greater than the plasma concentration.

- **Intergroup Trials** - Alberts et al reported on a randomized Intergroup (GOG/SWOG) trial in
small-volume stage III disease that compared intravenous vs intraperitoneal cisplatin, with all patients receiving IV cyclophosphamide as well.[42] There were two subsets of patients—those with residual disease (nodules or other deposits) measuring ≤ 0.5 cm after initial surgery (the subset in which one would anticipate that intraperitoneal therapy should be more effective), and those with residual disease > 0.5 cm and ≤ 2 cm. The intraperitoneal treatment arm was associated with a significant survival benefit (P = .02), but curiously, this benefit was not seen in the very small-volume cases (≤ 0.5 cm, P = .10).

A randomized, phase III Intergroup (GOG, SWOG, and ECOG) study[43] compared IV cisplatin (75 mg/m²) and paclitaxel (135 mg/m² over 24 hours) to IV carboplatin (dosed to an AUC of 9) followed by IV paclitaxel (135 mg/m² over 24 hours) and intraperitoneal cisplatin (100 mg/m²) in patients with optimally debulked disease. A superior recurrence-free survival time was noted in patients treated with intraperitoneal cisplatin (28 vs 22 months, P = .01), as well as an improvement in overall survival duration that was of borderline statistical significance (63 vs 52 months, P = .056). Since both intraperitoneal cisplatin and high-dose carboplatin were used in the experimental arm, it is not possible to conclude with confidence that the improvement resulted solely from intraperitoneal cisplatin. However, because the improvement in overall survival was of borderline statistical significance and toxicity was greater, the experimental arm is not recommended for routine use.

• GOG-172—Another phase III study of intraperitoneal therapy in advanced ovarian cancer is ongoing. In patients with optimally debulked disease, GOG-172 is comparing IV paclitaxel plus IV cisplatin as the standard treatment arm with IV paclitaxel plus intraperitoneal cisplatin and intraperitoneal paclitaxel as the investigational arm.

**Conclusions**

Parts 1 and 2 of this article have summarized the outcomes of major phase III trials in the field of gynecologic cancer. It is hoped that highlighting these randomized trials will assist clinicians in managing patients with these malignancies. In addition, we hope that these multidisciplinary approaches will foster further discussion and encourage innovative clinical trials in the future. Part of the challenge for the new millennium will be not only to refine current clinical research, but also to develop more effective and less toxic cytotoxic or biologic agents.

**References:**


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