The Management of Early Ovarian Cancer

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Approximately one third of patients with epithelial ovarian cancer present with localized or early-stage disease. Prognostic features identify certain subsets of patients with good risk characteristics who do not require adjuvant therapy.

Introduction

In the past year, ovarian cancer ranked as the fifth most common cause of malignancy among women in the United States [1]. There will be an estimated 21,000 new ovarian cancer cases this year, and approximately 13,500 deaths, which is more deaths than from endometrial and cervical cancers combined. Despite advances in cytoreductive surgery and dose-intensive combination chemotherapy, overall survival in patients with ovarian cancer has not changed in the past 2 decades, because more than two thirds of women continue to be diagnosed with advanced bulky disease. Patients with localized ovarian cancer, however, have been reported to have a 5-year disease-free survival of approximately 80% [2]. This article focuses on the management of early-stage ovarian cancer, which has been surgically defined by the staging system of the International Federation of Gynecologists and Obstetricians (FIGO) as stage I and stage II disease (Table 1).

Surgical Implications in Early-Stage Ovarian Cancer

Staging--Over the past decade, a great deal has been learned about the potential for occult extra-ovarian disease, which occurs in a significant proportion of women with apparent early-stage epithelial ovarian carcinoma. Comprehensive surgical staging is the single most important factor in deciding appropriate management of early-stage disease. It allows for a more accurate determination of prognosis and correctly identifies those patients whose survival may be improved by adjuvant therapy. The appropriate procedures that constitute a complete staging laparotomy for ovarian cancer are listed in Table 2 [3].

Unfortunately, many women who are explored for pelvic masses undergo their initial surgery in a community hospital by a general obstetrician/gynecologist or a general surgeon. Oftentimes, a comprehensive staging procedure is not performed, since ovarian cancer often is not suspected at the time of the patient's initial surgery. McGowan and coworkers [4] found that only 54% of 291 women with ovarian carcinoma had a complete comprehensive surgical staging at their initial laparotomy. In this series, 97% of the patients initially explored by gynecologic oncologists had complete surgical staging documented, compared with 52% and 35% of patients explored by obstetrician/gynecologists and general surgeons, respectively. In another series, only 25% of patients had an incision at the time of their initial surgery that would allow a thorough exploration and staging of the upper abdomen [5]. When a second laparotomy was performed, approximately 30% of the patients were upstaged, and approximately 75% of these patients actually had stage III ovarian carcinoma. Another study evaluated 59 women who were explored in a community hospital setting for a pelvic mass [6]. Only 15% had a comprehensive surgical staging procedure. Complete surgical staging was performed in 5% of cases managed by an obstetrician/gynecologist, and only 38% of patients were completely staged when a vascular surgeon was consulted.

Preoperative consultation with a gynecologic oncologist obviously is imperative. In addition, since age and menopausal status are important risk factors, we recommend that any patient who is peri- or postmenopausal and who has a pelvic mass should also have a gynecologic oncologist available at the time of her laparotomy, regardless of the value of the preoperative CA-125. Any postmenopausal woman with a pelvic mass and an elevated serum CA-125 level should be referred directly to a gynecologic oncologist for appropriate surgical staging and cytoreduction, as her risk of malignancy is exceedingly high (95%) [7].
Conservative Surgery--If an apparent stage IA ovarian carcinoma is encountered intraoperatively in a young woman desiring fertility, or in a woman whose desires are unknown, conservative surgery may be possible following careful inspection of the upper abdomen and retroperitoneum. The contralateral ovary should also be carefully inspected. Unless an obvious lesion is noted, random biopsies or wedge resections are not recommended, because they may compromise future fertility. If, on gross inspection, there appears to be no extra-ovarian disease, the surface of the ovary is smooth without excrescences, and there are no adhesions between the mass and the pelvic side walls, then a unilateral salpingo-oophorectomy with adequate resection of the ipsilateral infundibulopelvic ligament may be performed. A thorough surgical staging procedure as shown in Table 2 should be undertaken, except that the contralateral ovary and uterus are not removed. If, on the final histopathology review, adverse prognostic factors are discovered, the benefits of a second operation to remove the uterus and the retained ovary may be discussed and safely performed after careful consideration has been given to every alternative. Consideration should be given to a "completion" total abdominal hysterectomy and unilateral salpingo-oophorectomy following the patient's childbearing, although it has not been established that there is any benefit from this procedure.

Although not common, early epithelial ovarian carcinoma does occur in younger women who have not completed childbearing. In these circumstances, it is crucial to review with the patient, prior to surgery if possible, the risks and possible benefits of conservative surgery with preservation of reproductive function. Several studies have documented compromised survival for patients with stage I ovarian carcinoma treated with unilateral salpingo-oophorectomy. In one series, the contralateral ovaries of 65 women with apparent stage IA ovarian carcinoma were pathologically evaluated, and 14% had cancers in the normal-appearing ovary [8]. Additional reports have documented poor survival in women undergoing unilateral oophorectomy (50%), compared with women undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy and complete comprehensive surgical staging (80%) [9]. These studies are flawed by nonrandomized small numbers of patients, many of whom did not have comprehensive surgical staging. In contrast, Williams and coworkers [10] retrospectively reviewed 29 patients with apparent stage I ovarian carcinoma treated with unilateral salpingo-oophorectomy. No recurrences were documented after initial surgery in 19 patients with grade 1 or 2 lesions that did not have capsular rupture, pelvic adhesions, or surface excrescences. Among these 19 patients, seven were successful in achieving pregnancy. If the dominant ovarian mass was adherent, ruptured, or had excrescences, 50% of these patients eventually died.

Ovarian Tumors of Low Malignant Potential--Borderline tumors of the ovary or tumors of low malignant potential constitute a distinct, well-defined pathologic entity with several characteristic microscopic findings that distinguish it from its invasive counterpart. These tumors have characteristic papillary fronds, epithelial tufts, and a pseudostratification of their nuclei, but do not exhibit any stromal invasion microscopically. Clinically, borderline tumors are more indolent than typical ovarian cancers.

Unlike invasive epithelial ovarian cancer, approximately 75% of these tumors are diagnosed in early stages and represent approximately 15% of all ovarian malignancies. If these tumors are encountered intraoperatively, a gynecologic oncologist should be consulted, and every effort should be made to fully stage the patient, just as in invasive epithelial ovarian cancer. It should be noted, however, that these cancers are not usually chemosensitive, and the surgeon should attempt to remove all gross evidence of disease. In younger women who desire the preservation of their fertility, conservative surgery should be attempted in exactly the same fashion as previously described for women with invasive early epithelial ovarian cancers who desire preservation of their childbearing potential. Recurrence rates are higher in women who have conservative surgery than in women who have definitive surgery, but there is no difference in overall survival, due to effective salvage surgery.

In one series, approximately 24% of apparent early-stage epithelial ovarian cancers of low malignant potential were upstaged by a comprehensive surgical staging procedure [3]. Obviously, upstaging has important prognostic implications, though not as significant as with invasive disease. In addition, an experienced gynecologic pathologist should be consulted in all cases because of the unusual nature of the tumor and the difficulty in making accurate diagnoses and differentiating it from its malignant counterpart. Clinicians should be aware that appropriate sampling of large pelvic masses includes at least one pathologic section for every centimeter of the mass. Of equal importance is the fact that the diagnosis of a tumor of low malignant potential in the operating room by frozen section does not confer the same accuracy as diagnosis of an invasive tumor or a benign tumor by frozen
section. It is therefore of utmost importance to completely stage the patient in a thorough fashion at the time of the initial surgery, as a percentage of these cancers thought to be of borderline histology intraoperatively will be documented as invasive on final pathologic review. Although the prognosis for patients with tumors of low malignant potential is much better than for patients with invasive tumors, approximately 10% of stage I tumors will ultimately recur. Because these tumors are indolent, recurrences can present 10 to 15 years after the initial diagnosis, making long-term follow-up necessary. Surgical reexploration should be strongly considered in these patients when recurrence is suspected, since long-term palliation and even cure have been documented after secondary surgical resection [11,12].

Laparoscopic Management of Adnexal Masses--Because of advances in minimally invasive surgery, laparoscopic management of ovarian masses has important considerations in the discussion of early ovarian cancer. Older series [13,14] have documented an adverse effect of tumor rupture in patients with stage I ovarian cancer, although these findings have not been confirmed in more recent series using more elaborate statistical methods [15]. It should be noted that most patients in these studies received adjuvant therapy after tumor rupture was documented, and this "adjuvant" treatment may have negated, in part, the adverse prognostic effect of tumor spill at the time of surgery. Despite the lack of convincing data suggesting adverse outcomes in patients with tumor rupture, adjuvant therapy is often given in cases of rupture, due to the oncologist's bias or perhaps the bias written into protocols for early ovarian carcinoma. All this considered, difficult dissections performed laparoscopically are likely to result in tumor rupture. In addition, laparoscopic surgery has a disadvantage in that the surgeon loses the ability to carefully palpate and inspect all of the peritoneal surfaces. Patients of any age group with an elevated CA-125, or with suspicious findings on ultrasonic examination (abnormalities within the cyst wall, septations, or any solid component), should be managed with exploratory laparotomy, unless they have consented to an investigational protocol for evaluating pelvic masses laparoscopically. It should be apparent to any clinician that loss of the ability to palpate and inspect the entire abdominal cavity and retroperitoneum could significantly compromise the accuracy of the surgical staging procedure and be detrimental to the patient's prognosis.

Second-Look Laparotomy--Previously, operative reexploration was an integral part of the management of advanced ovarian carcinoma. Although this procedure helped physicians decide whether to discontinue chemotherapy or to use additional therapeutic regimens, it has not contributed to improvement in survival. Traditionally, second-look laparotomy was considered for patients with advanced disease, but several studies have now evaluated this procedure in patients with early ovarian cancer [16,17]. Walton and coworkers [16] evaluated the experience of the Gynecologic Oncology Group (GOG) in 112 patients who underwent initial surgical staging and had FIGO stage I and II ovarian carcinomas documented histologically. Following adjuvant therapy, these patients then underwent a restaging operation. Of 95 patients who were asymptomatic prior to their second-look laparotomy, only 5% had disease confirmed by second-look laparotomy, as opposed to over half of 17 patients who were symptomatic prior to their second-look laparotomy. These data suggest that for asymptomatic patients with early-stage disease, in whom initial comprehensive surgical staging was performed and followed by adjuvant therapy, routine second-look surgery will yield positive results in only a small percentage of patients. Therefore, routine use of second-look laparotomy is not recommended.

_good Prognosis Patients_

Prognostic features, such as histologic grade and cell type, ascites, peritoneal cytology, and extent of disease, allow separation of patients with early-stage ovarian cancer into groups at low and high risk for relapse. The separation of risk groups is largely based on the findings of thorough and comprehensive surgical staging.

The largest randomized trial involving good prognosis patients was conducted by the GOG [2]. Eighty-one patients with stage IA or IB disease with well or moderately differentiated tumor (grade 1 or 2) after comprehensive surgical staging were randomized to receive either no treatment or melphalan (Alkeran). On subsequent pathologic review, one third of the patients had borderline tumors, but these patients were equally distributed between the two arms. The median follow-up was in excess of 6 years. There was no significant difference in the 5-year disease-free survival (91% for no treatment versus 98% for melphalan) or overall survival (94% versus 98%, respectively). Three of eight patients (38%) who had clear cell tumors relapsed, compared with only two of 63 patients (3%) with other known histologies. The overall acute toxicity from melphalan was easily
manageable. Sixteen percent of patients developed significant myelosuppression, as defined by a platelet count less than 50,000/mcL or a white blood cell count less than 2,000/mcL. There were no episodes of neutropenic fever or bleeding as a consequence of treatment. Mild gastrointestinal toxicity was observed in 26% of patients. One patient developed the long-term complication of aplastic anemia, but there were no cases of leukemia. However, other trials have clearly documented the leukemogenic potential of chronic alkylating agent therapy in ovarian cancer [18].

From these data, patients without ascites who have stage I disease and low-grade tumors do not require adjuvant chemotherapy after primary surgical debulking, with the possible exception of those whose tumors have clear cell histology, which seems to portend a worse prognosis. Many retrospective analyses are consistent with this randomized trial. Investigators at the National Cancer Institute of Canada followed 68 evaluable patients with stage IA to IC disease who did not receive adjuvant treatment after primary cytoreductive surgery and staging [19]. Lymph node biopsies were recommended but were not required. There were three recurrences, with one death due to disease. There was an obvious lack of high-grade (grade 3) lesions (n = 3), which could have influenced the study outcome. The paucity of grade 3 patients was probably due to physician reluctance to withhold treatment from this group of patients. Forty patients had stage IA or IB disease with well or moderately differentiated tumors without cytologically positive ascites or washings. Only one recurrence occurred in this group (with clear cell histology). The other two recurrences had clear cell histology and/or dense adhesions. Even though second-look surgery was not performed, an excellent clinical outcome was still achieved, with a 3-year actuarial disease-free survival of 94%. The median follow-up was 4 years. As emphasized in the editorial accompanying this report, more nonrandomized trials are not likely to “advance the field,” since events (death and recurrences) are relatively uncommon, and thus small selection biases can markedly affect a trial's results and conclusions [20].

A retrospective review of 252 patients with stage I epithelial ovarian cancer from the Princess Margaret Hospital identified histologic grade as the most powerful predictor of relapse, followed by dense adhesions and large volume ascites [15]. These prognostic factors were then validated using a separate population of 267 patients from the Norwegian Radium Hospital. Patients with dense adhesions had treatment outcomes similar to those of patients with stage II disease. Substage (bilaterality or capsule integrity), histologic cell type, age, time from diagnosis, and postoperative therapy did not predict relapse. The 5-year relapse-free survival for patients with grade I tumors without dense adhesions or large volume ascites was 98%. For all stage I patients, the 5-year relapse-free survival was 79%. The strengths of this study, despite being retrospective, are validation of the identified factors on a separate population, large size, and pathology review to confirm histologic features.

Similar findings were reported by Sevelda and colleagues [21] in a retrospective review of 204 patients with stage I ovarian cancer (borderline tumors were excluded); a multivariate analysis revealed that only histologic grade and the extent of surgery significantly influenced survival. Forty-one patients underwent only unilateral salpingo-oophorectomy, because malignancy was not diagnosed intraoperatively and the patient refused reexploration. This group of patients had a significantly reduced 5-year survival (62%), compared with patients who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without omentectomy (84%). Even this latter group was probably understaged, since not all patients had omentectomy, lymph node biopsies, and/or washings routinely performed, compromising the interpretation of the survival data. Nearly one half (48%) of the patients were staged as IAI and received no treatment. Patients of higher stage or grade received whole abdominal radiation (n = 115) or chemotherapy (n = 22). Only 18 patients (8.8%) had stage IC disease, which favorably influenced the survival data. There were 33 deaths due to disease, with an overall 5-year survival of 79.1% (82.5% for patients receiving no treatment and 78.9% for patients receiving whole abdominal radiation or chemotherapy).

A multicenter Dutch trial followed 67 evaluable patients with early-stage, well-differentiated ovarian cancer after primary surgery but without further treatment [6]. A relatively large number (19) were found to be ineligible because histologic classification could not be confirmed. The mean follow-up was 50 months. Only 35.8% (24 patients) had complete surgical staging. The 5-year disease-free survival of the group that was completely staged was 100%. The 5-year disease-free survival for the remaining patients was 88%. There was no statistical difference between the disease-free survival of these two groups, due to the small number of patients with recurrences (n = 4). Patients with grade 1 stage IA to IIA ovarian cancer had an excellent prognosis. It is now evident that patients with disease localized to the ovaries and favorable histology require no adjuvant treatment (Table 3). Patients who have tumor characteristics other than those described in Table 3 are considered at high
risk for recurrence and should receive adjuvant therapy.

**Improving Objectivity of Assessing Prognosis**

While tumor grade influences the risk of relapse, it is subject to high intra- and interobserver variability. More quantitative and reproducible techniques for assessing prognosis are needed. Morphometric features and cellular DNA content have been evaluated. These indicators were applied to 33 patients with stage I ovarian cancer with 5 or more years of follow-up [22]. The overall survival for these 33 patients was 64%. Three categories of risk were determined, based on two easily measured morphometric features, the mitotic activity index (MAI) and the volume percentage of epithelium (VPE). The mitotic activity index is defined as the number of mitotic figures within the neoplastic epithelium in a defined number of high-powered fields selected randomly from the most atypical areas of the tumor. The volume percentage of epithelium is the volume percentage of the neoplastic epithelium in a microscopic field. Patients in category A (MAI < 30, VPE < 65), category B (MAI < 30, VPE 65 or greater), and category C (MAI 30 or greater) had 5-year overall survival rates of 91%, 67%, and 38%, respectively. Each category contained only nine to 13 patients. Twenty-five of 33 patients had diploid tumors. The 5-year overall survival for these patients was 68%, compared with 37% for the patients with aneuploid tumors. No patient in category A had an aneuploid tumor. Patients in category C with aneuploid tumors (seven patients) had a worse 5-year survival than those category C patients whose tumors were diploid (six patients), 29% versus 50%, respectively. In patients with aneuploid tumors, morphometric features did not influence survival. However, in diploid tumors, morphometric features had additional prognostic value. The survival rates of patients with diploid tumors in categories A, B, and C were 91%, 63%, and 50%, respectively. While morphometric features and DNA content seem to have predictive value, no statistical analyses were reported, probably due to the small number of patients in each group.

Other investigators evaluated the same parameters of morphometric and DNA content in 64 patients with well-differentiated stage I A to IIA ovarian cancer treated at multiple institutions [23]. The median follow-up was 60 months, with 42% of patients surviving 60+ months. Only 23 of the 64 patients had accurate staging. Five patients had recurrences, all of whom were incompletely staged. Forty-two tumors had a mitotic activity index less than 30 and 43 patients had a volume percentage of epithelium less than 65. Neither of these morphometric features alone or in combination correlated with 3- and 5-year survival. Other parameters, including menopausal status, FIGO stage, and histologic cell type, had no impact on 3- and 5-year survival. A high-risk group of patients with aneuploid tumors was identified. These patients with a DNA index of greater than 1.4 had a poor outcome. Only two of 32 patients with diploid tumors relapsed at 25 and 40 months after primary surgery. Three of the eight patients with a DNA index of greater than 1.4 relapsed at 11, 34, and 34 months after primary surgery. Once DNA content was considered, no other factor was predictive of outcome in these patients with early-stage, low-grade disease.

Other studies also have demonstrated that DNA ploidy is of prognostic significance. Kallioniemi and colleagues [24] retrospectively analyzed tumor samples from 157 patients with ovarian cancer by flow cytometry. The relative risk of death was twofold higher in patients whose tumors had a single aneuploid cell population and sixfold higher in patients whose tumors had multiple aneuploid cell clones, compared with patients with diploid tumors after adjusting for stage, residual tumor mass, histologic cell type, treatment, grade, and patient age. Tumors with a DNA index greater than 2.2 were highly aggressive. The S-phase fraction also had prognostic value in diploid tumors. The DNA index, number of aneuploid cell clones, and S-phase fraction were more prognostic than ploidy alone. High-risk characteristics were multiple aneuploid cell populations or DNA aneuploidy combined with a high DNA index (greater than 2.2) or high S-phase fraction (greater than 16%). All patients with multiploid tumors, including those with stage I disease, died within 3 years of diagnosis. Multiploidy may be a reflection of genomic instability and increased likelihood of developing drug-resistant clones. Low-risk tumors were diploid with a low S-phase fraction (less than 9%). The remainder constituted an intermediate-risk group. The prognostic values of mitotic count and nuclear grade were inferior to DNA flow cytometry. In a multivariate analysis, only stage, ploidy, S-phase fraction, and histologic cell type (undifferentiated carcinoma) emerged as independent prognostic factors. Histologic cell type did not correlate with ploidy. In this study, all borderline tumors were diploid. However, in another large study, aneuploid borderline tumors were detected and found to have a worse prognosis [25].

Two more recent reports confirm the importance of DNA ploidity as an independent prognostic characteristic in early-stage ovarian cancer [26,27]. Investigators at the Norwegian Radium Hospital
used flow cytometry to analyze samples from 279 evaluable patients with stage I invasive ovarian cancer [26]. The overall 5-year disease-free survival of this patient population was 78%, which is similar to other trials. The median follow-up was 60 months, with a median time to relapse of 16 months. Approximately one half (49%) of these stage I patients had nondiploid tumors. Seventy-seven patients with stage I, grade 1, diploid tumors had no relapses. There were 62 relapses in the remaining 202 patients. Grade did not always correlate with ploidy, since 32% of grade 1 tumors were nondiploid. Patients with clear cell histology did poorly independent of ploidy. In patients with clear cell histology, substage was the most important predictor of relapse.

Gajewski et al [27] retrospectively examined tumors from 87 patients by flow cytometry. Only 19 of these patients had early-stage disease. Nine patients with diploid tumors had 100% survival at 96 months median follow-up. Ten patients with aneuploid tumors had a survival of 58% at 65 months median follow-up. Flow cytometry establishing DNA ploidy appears to have independent prognostic value in patients with early-stage ovarian cancer and needs to be studied in prospective, randomized clinical trials.

**Adjuvant Chemotherapy Trials**

Patients with ovarian cancer can be divided into good or poor groups based on clinical and pathologic features already reviewed. Those patients with favorable characteristics, such as stage IA or IB, grade 1 or 2 tumors, require no further treatment after cytoreductive surgery and comprehensive staging. The remainder of patients with early-stage disease have, at best, an overall 5-year survival of 80% when fully staged and treated with some form of adjuvant therapy [2]. Cisplatin (Platinol)-based chemotherapy has been the cornerstone of treatment for patients with ovarian cancer after primary surgery. In advanced disease, response rates up to 90% have been achieved [18]. Hence, there has been great interest in studying platinum-based chemotherapy in early-stage disease.

The only randomized trial with a no-treatment arm is being conducted by the Italian Interregional Cooperative Group of Gynecological Oncology [28]. It compares cisplatin (50 mg/m² every 28 days for six cycles) with no treatment in patients with stage IA or IB, grade 2 or 3 tumors. Thus far, the 5-year disease-free survival for the cisplatin arm is 81% versus 61% for the control arm, with a median follow-up of 60 months. The overall survival is similar between the two arms, 85% versus 86%, due to the efficacy of platinum-based salvage chemotherapy at the time of relapse for patients in the control arm. Final data analysis of this trial will help determine if adjuvant cisplatin chemotherapy improves the outcome of patients with early-stage ovarian cancer.

Multiple phase II trials of cisplatin-based regimens have been reported (Table 4) [29-36]. In general, the toxicities of short-term (usually six cycles) platinum-based chemotherapy, including mild to moderate nausea, emesis, and myelosuppression, were easily managed. Long-term sequelae of nephrotoxicity, neurotoxicity, and ototoxicity were not observed. Overall, the long-term toxicity of such treatment was less severe than the risks of prolonged alkylating agent therapy (leukemia) or irradiation (radiation enteritis).

While these studies all involve small numbers of patients, it seems clear that patients with high-grade tumors have a poor prognosis. In most of these trials, patients with stage I, grade 1 or 2 disease are represented in small numbers. A larger number of such patients were included in the trial by Piver et al [31], which yielded a 5-year relapse-free survival of 93%. Twenty of the 30 stage I patients had grade 1 or 2 histology and might have done well without further therapy after primary surgery, as was demonstrated by the GOG trial randomizing between observation and melphalan [2]. Stage also was predictive of a poor outcome, though not in every study. One reason for the lack of uniformity of the prognostic value of stage is that some studies had a high predominance of stage IC patients, known to be at high risk, within the stage I group, while other trials had very low numbers of these patients. Data from Piver and associates [30] showed that patients with stage II disease did worse than patients with stage I disease treated with the same regimen. For stage II patients, these regimens are no more effective than pelvic irradiation plus melphalan or whole abdominal radiation, which have estimated 5-year survival rates of 50% and 40%, respectively. All of the studies listed in Table 4 are flawed by the lack of uniform complete surgical staging, which hinders the ability to draw solid conclusions.

**Intraperitoneal Administration**--Ovarian cancer provides an excellent model for the intraperitoneal route of chemotherapy administration, since this disease disseminates primarily by peritoneal seeding [37]. The intraperitoneal administration of chemotherapy usually is associated with a pharmacologic advantage over intravenous administration, but no prospective randomized
trials have demonstrated a survival advantage for the intraperitoneal route compared with the intravenous route. Responses are not commonly seen with intraperitoneal platinum chemotherapy in patients with tumor nodules greater than 0.5 cm to 1 cm in maximum diameter. Most responses have been observed in patients in whom intravenous platinum-based chemotherapy also was associated with significant response rates. Carboplatin (Paraplatin) was developed as a less toxic alternative to cisplatin. The results of a recent metaanalysis showed no difference in survival between cisplatin- and carboplatin-treated patients with advanced disease. These results were confirmed by two large randomized prospective trials conducted by the Southwest Oncology Group and the National Cancer Institute of Canada [38].

**Intraperitoneal Carboplatin**—Malmstrom et al [39] conducted a phase I trial of intraperitoneal carboplatin as adjuvant treatment for patients with early-stage ovarian cancer. This form of treatment is most likely to be effective against small volume disease, and thus is a rational approach for study as treatment for localized disease. Compared with intravenous administration, intraperitoneal carboplatin had minimal local toxicity and a favorable pharmaco-kinetic advantage, with a peak peritoneal cavity/peak plasma concentration ratio of approximately [18]. The dose-limiting toxicities in this phase I intraperitoneal carboplatin trial were thrombocytopenia and leukopenia. The maximum tolerated dose was 500 mg/m² every 28 days. No response data were reported. These investigators are evaluating this form of treatment for early-stage ovarian cancer in a phase II trial.

**Taxol**—Paclitaxel (Taxol) is an antineoplastic drug recently licensed for use in patients with platinum-refractory ovarian cancer. It has a novel mechanism of action, which is to promote polymerization of microtubular proteins, rendering them resistant to disassembly, thereby disrupting mitosis. In early phase II trials in platinum-refractory disease, paclitaxel achieved approximately a 30% response rate. Recent data from a large randomized trial comparing cisplatin plus cyclophosphamide (Cytoxan, Neosar) with cisplatin plus paclitaxel in previously untreated patients with advanced ovarian cancer showed that the patients who received the paclitaxel-containing regimen had a higher response rate and longer disease-free survival [38]. A phase I pilot study from the Fox Chase Cancer Center evaluated the combination of carboplatin and paclitaxel in previously untreated patients with advanced disease [38]. Carboplatin dosing was based on the Calvert formula. The dose-limiting myelosuppression occurred with a carboplatin dose at a target AUC (area under the concentration versus time curve) of 10 plus a fixed dose of paclitaxel at 135 mg/m² administered over 24 hours. The maximum tolerated dose of carboplatin with this dose of paclitaxel is at a target AUC of 7.5. If the combination of paclitaxel with a platinum analog proves to be superior therapy in advanced disease, such a combination would need to be tested in patients with early-stage disease, in whom a low tumor burden may yield even better results. The combination of paclitaxel (1.75 mg/m²) and carboplatin (AUC = 7.5) for three versus six cycles as an outpatient regimen will be evaluated in the next GOG trial proposed for early-stage ovarian cancer. The intraperitoneal route of administration is actively being explored for paclitaxel. Its relatively high molecular weight and bulky structure would result in a slow exit from the peritoneal cavity. The pharmacokinetics of paclitaxel are highly favorable for the intraperitoneal route, where the drug exposure to the peritoneal cavity exceeds that of the plasma by approximately 1,000-fold [40]. Phase II trials of intraperitoneal paclitaxel for advanced disease are in progress. If successful in advanced disease, this form of therapy may also be effective in previously untreated patients with early-stage disease with smaller tumor burdens.

The role of adjuvant chemotherapy for early-stage ovarian cancer can only be defined in randomized prospective trials. Although phosphorus 32 has been shown to be superior to melphalan because of a more favorable toxicity profile, 20% of patients still died of disease [2]. This improvement in the death rate over earlier trials is primarily due to better staging. As a result, the contribution of adjuvant chemotherapy has been difficult to assess and will require trials with a no-treatment arm. However, because of the high mortality rate, many investigators have been reluctant to perform clinical trials with a no-treatment arm. The ongoing International Collaboration Ovarian Neoplasm (ICON) trial for early-stage disease compares immediate platinum-based chemotherapy with deferral of chemotherapy until disease is detected [41]. The Italian study comparing cisplatin with observation has shown a significant improvement in 5-year relapse-free survival for patients receiving cisplatin [28]. Such trials will definitively evaluate the role of adjuvant platinum-based treatment in early-stage disease.

**Radiation Therapy**
Traditionally, two modalities have been available to radiation oncologists in the management of ovarian cancer: radiocolloid treatment and external beam radiation therapy. Although divergent in their mechanisms of action, each of these approaches can address the failure patterns of ovarian cancer within the abdomen and pelvis. The technical considerations and clinical experiences associated with these respective options will be detailed separately. While the focus of the present review concerns early-stage ovarian cancer, many published series include patients with stage I to III tumors. Where possible, data on the early-stage patients will be extracted for presentation; however, sometimes only the data from the entire range of patients could be gleaned from the reports as published.

**Intraperitoneal Radioactive Chromic Phosphate Suspension**—The pioneering work with radioactive colloids employed gold 198. More recent studies utilized phosphorus 32 because of a higher beta energy, which allowed greater tissue penetration without gamma radiation, thereby causing fewer complications [42]. The radiation emitted by phosphorus 32 is in the form of electrons, with an average tissue penetration range of 1.4 to 3.0 mm and an average energy of 0.69 MeV [42]. The protocol of instillation and distribution of phosphorus 32 is complex. After instillation of phosphorus 32, patients are placed in various positions (Trendelenburg, supine, prone, left/right lateral decubitus, and reverse Trendelenburg) to assure adequate distribution over peritoneal surfaces [43]. Intraperitoneal isotope distribution is tested prior to instillation with radioactive technetium sulfur colloid or after radiocolloid administration with scintigraphic imaging of Bremsstrahlung photons [43,44].

Vergote et al [44] reported the direct imaging of phosphorus 32 in 297 patients by using a gamma camera to detect the Bremsstrahlung photons generated by the emitted phosphorus 32 electrons. Images were obtained 2 to 24 hours and 3 to 7 days following administration of phosphorus 32. Uneven distribution (areas with major accumulation or very low activity of the isotope) was observed in 16% of patients, loculation in 2%, leakage in 3%, and uptake in thoracic lymph nodes in 54%. Major accumulation of the isotope was observed in the pelvis (60%) and in the right flank (33%) for patients with uneven distribution. An even distribution 2 to 24 hours after instillation did not exclude the presence of major accumulation 3 to 7 days later in 46% of patients. There was no relationship between uneven distribution, loculation, or leakage of intraperitoneal phosphorus 32 and relapse or bowel obstruction.

Walton et al [43] described the GOG experience with phosphorus 32 in early ovarian cancer and reported that only 5.4% of patients could not receive phosphorus 32 because of uneven distribution of technetium (n = 1) or inability to gain access to the peritoneal cavity (n = 3), even though the time to instillation ranged from 5 to 106 days after definitive surgery. The minor complications associated with phosphorus 32 in the GOG experience were abdominal pain after intraperitoneal injection (19%) and peritonitis (3%). Severe complications requiring surgery occurred in 7% of patients due to either injury to bowel after catheter placement (n = 1) or small bowel perforation/obstruction (n = 4), with a mean follow-up of 12 months [43]. Klaassen et al [45] and Pezner et al [46] observed a significant increase in complications to small bowel when external pelvic irradiation was combined with intraperitoneal isotope phosphorus 32. The precise distribution of phosphorus 32 intra-abdominally is unknown. Abdominal distribution includes lymphatic absorption by peritoneal surfaces or by macrophages lining the peritoneal cavity, with high concentrations in infradiaphragmatic regions, contiguous thoracic lymph nodes, and omentum [42,47]. Pelvic and para-aortic lymph nodes receive relatively low nontherapeutic doses [47]. The precise dose of phosphorus 32 delivered to the peritoneal surfaces is also unknown, although it appears that with strict adherence to technique, an "almost uniform therapeutic dose" can be achieved [47].

**Randomized Trials Including Phosphorus 32**—The initial GOG experiences with early-stage, high-risk ovarian cancer after complete surgical staging was reported by Young et al in 1990 [2]. The study included 141 eligible patients with poorly differentiated cancers confined to the ovaries; cancers with capsular penetration, ascites, or positive peritoneal cytology; or resectable stage II disease after complete surgical staging. Patients were randomized to receive either phosphorus 32 (15 mCi) or melphalan (0.2 mg/kg body weight/day for 5 days, repeated every 4 to 6 weeks for up to 12 cycles). The disease-free survival rate was 80% in each arm, with no statistical difference between groups in 5-year overall survival rate with a median follow-up greater than 6 years. Although there was no observation arm for this high-risk group of early-stage ovarian cancer patients, the GOG concluded that the added cost, inconvenience, and risk of late leukemia from melphalan were not justified, and phosphorus 32 was chosen as the control arm for the next GOG trial.
The management of early ovarian cancer

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The current GOG trial randomizes this high-risk group of early ovarian cancer patients after complete surgical staging to receive either intraperitoneal phosphorus 32 (15 mCi) or cyclophosphamide (1 g/m² IV) plus cisplatin (100 mg/m² IV) every 21 days for three cycles. With a median follow-up in this trial of 14 months, interim results have been reported, with seven recurrences in each arm at 6 to 21 months, and a median time to recurrence of 14 months (for these 14 patients) [48]. The median time to recurrence for either arm as a whole has yet to be reached.

The National Cancer Institute of Canada Clinical Trials Group randomized 257 eligible patients with high-risk stage I, stage II A (high-grade, capsular penetration, positive cytology, cyst rupture), or completely resected stage IIB or III disease to receive abdominal pelvic irradiation by moving-strip technique (2,250 cGy/20 fractions), melphalan (8 mg/m²/day for 4 days every 4 weeks for 18 cycles), or phosphorus 32 (10 to 20 mCi) following pelvic radiation therapy (2,250 cGy prior to abdominal irradiation; 4,500 cGy prior to melphalan or phosphorus 32) [45]. All patients had abdominal hysterectomy, but the extent of surgical staging was not mandated by study design. Pretreatment characteristics included 9% borderline tumors, 14% clear cell, 31% grade 3, and 5% stage III.

With a median follow-up of 8 years, actuarial 5-year survival rates were not significantly different for the abdominal pelvic irradiation, melphalan, and phosphorus 32 arms (62%, 61%, and 66%, respectively). The phosphorus 32 arm was closed prematurely secondary to a high incidence of delayed bowel complications. Protocol violations in covering the whole abdominal target volume correlated with reduced survival in a multivariate analysis [45].

Vergote et al [49] of the Norwegian Radium Hospital reported a randomized trial of 340 completely resected stage I, II, and III ovarian cancer patients, comparing cisplatin (50 mg/m² for six courses) with intraperitoneal phosphorus 32 (7 to 10 mCi, depending on patient weight). Patients randomized to phosphorus 32 with extensive adhesions were treated with abdominal pelvic irradiation instead of phosphorus 32 (17%). Surgical staging included hysterectomy/bilateral salpingo-ophorectomy, infracolic omentectomy, evaluation of ascitic fluid (but not peritoneal washings), pelvic/paraortic lymphadenectomy, and biopsies of the diaphragm. Pretreatment characteristics included 20% borderline tumors, 14% clear cell, 23% grade 3, and 8% stage III.

The 5-year actuarial disease-free survival rates, with a median follow-up of 62 months, did not differ significantly between the cisplatin group (75%) and the phosphorus 32 group (81%). Although no survival benefit was apparent for cisplatin over phosphorus 32, a significant reduction in bowel obstruction was demonstrated. This may be related to technique, since peritoneal distribution was not verified by technetium prior to instillation of phosphorus 32. However, the 5% rate of surgically treated small bowel obstruction after phosphorus 32 administration was comparable to the GOG experience. Therefore, the Norwegian group recommended cisplatin as standard adjuvant treatment for subsequent studies.

Pecorelli et al [28] reported preliminary data from a multicenter randomized trial for stage IC ovarian cancer that compared cisplatin (50 mg/m² every 28 days for six cycles) with phosphorus 32 (12 mCi). Complete surgical staging was required, with the exception of retroperitoneal lymph node evaluation, which could be performed by biopsy, lymphangiogram, or computed tomography scan. Phosphorus 32 distribution was evaluated by technetium scan. With a median follow-up of 60 months, disease-free survival was prolonged in the cisplatin group, compared with the phosphorus 32 group. There was no difference in 5-year survival (cisplatin, 80%; phosphorus 32, 78%). Longer follow-up is necessary to assess the ability of cisplatin to salvage patients on the phosphorus 32 arm, which may affect long-term survival. The efficacy of paclitaxel for the salvage of cisplatin-treated patients was not assessed in this trial.

Additional retrospective studies of phosphorus 32 in early ovarian cancer support the low recurrence rates for this group of patients, as well as the difficulty with comparison of retrospective and prospective studies because of differences in prognostic factors and completeness of surgical staging [44,46,50-52]. The prospective randomized trials that included phosphorus 32 are summarized in Table 5.
External Beam Irradiation: Clinical Outcome--In the treatment of ovarian cancer, external irradiation should be directed to the abdomen and the pelvis. Two studies have shown that transperitoneal spread is the most common route for dissemination of ovarian cancer [53,54]. The GOG randomized surgically debulked (though not surgically staged) patients with stage I disease to observation, melphalan, or pelvic irradiation [53]. Although 186 patients were enrolled in that study, only 86 were evaluable, rendering the respective treatment arms unequally matched for prognostic variables. Neither of the adjuvant treatment arms significantly reduced the recurrence rate when compared with the observation arm. Similarly, in a two-arm randomization from the Princess Margaret Hospital, pelvic irradiation had no impact on the rate of relapse or survival, when compared with observation, for patients with stage I disease [54]. The focus of clinical investigation was therefore shifted toward treatment of the entire abdomen as well as the pelvis.

In a prospective trial conducted at the Princess Margaret Hospital [55], patients with stage I to III disease were randomized to either abdominopelvic irradiation or pelvic irradiation, alone or followed by chlorambucil (Leukeran). Among those with minimal (less than 2 cm) or no residual disease, there was a statistically significant benefit in 10-year survivorship favoring the abdominopelvic radiation group (64% vs 40%; \( P = .0007 \)). At Princess Margaret Hospital, the survival benefit did not apply to patients with gross disease (2 cm or more) remaining after laparotomy. In a retrospective analysis of postoperative radiotherapy for patients with stage I to IIIA cancers and 2 cm or less of residual disease, Fuller et al [56] observed a 71% 10-year relapse-free survival rate among those treated by abdominopelvic irradiation, compared with 40% relapse-free survival when subtotal abdominopelvic techniques were used (\( P \) being .02 or less). In that study, the survival benefit was even more pronounced (\( P < .003 \)) when the comparison was adjusted for differences in stage, grade, and volume of residual disease. Other institutional experiences attesting to the efficacy of abdominopelvic irradiation are available from Yale (77% 10-year survival among stage I to III patients) and Walter Reed Army Medical Center (78% 10-year survivorship among optimally debulked stage II patients) [57,58].

Not all investigators have been able to reproduce the favorable abdominopelvic irradiation results of the institutions listed above. In a trial from the University of Texas M.D. Anderson Cancer Center, patients with stage I and II disease were randomized to receive either 12 cycles of melphalan or abdominopelvic irradiation [59]. Although no survival differences were evident between the two arms (Table 6), several caveats about this study should be noted: First, the median follow-up was short, and the data have never been updated in peer-reviewed format, thus preventing the detection of additional failures or melphalan-induced leukemias. Second, the randomization was conducted without stratification for stage, grade, and residual volume of disease. Third, the number of abdominal failures among the patients treated with abdominopelvic irradiation may have been increased, since planning was not carried out with fluoroscopic simulation. As such, all diaphragmatic surfaces were not necessarily encompassed throughout respiratory excursion. Finally, the moving-strip technique as used at M.D. Anderson Cancer Center was associated with significant treatment interruptions (1 week or more) in 10% of irradiated patients. It is possible that optimization of abdominopelvic irradiation would have allowed the delivery of more biologically effective continuous therapy to a greater percentage of patients.

In a randomized study of abdominopelvic irradiation versus pelvic irradiation plus cyclophosphamide in the treatment of patients with stage I and II disease, Sell et al [60] saw no difference between the regimens with respect to 4-year survival (63% for abdominopelvic irradiation versus 55% for pelvic irradiation plus cyclophosphamide). Moreover, when they restricted their analysis to the intermediate-risk group (eg, stages II to III, with 2 cm or less of residual disease), which benefited most from abdominopelvic irradiation in the model of Dembo [55], Sell et al could not isolate a survival advantage among those treated with abdominopelvic irradiation. Macbeth et al [61] used the Princess Margaret Hospital technique to treat 57 women with early-stage disease (49%, stage I; 44%, stage II; 7%, stage III). For the entire series, the actuarial 5-year relapse-free and overall survival figures were only 49% and 56%, respectively. The data from the Curie Memorial Institute in Poland [46] are often quoted in the context of negative trials [62]. In their report, Reinfuss et al [62] described a 40% overall cure rate among stage I to III women with 3 cm or less of residual disease. Although these results are ostensibly inferior to those of Dembo and others, Reinfuss et al did not separately analyze patients with less than 2 cm of residual disease who were treated by abdominopelvic irradiation. In addition, a trend favoring abdominopelvic irradiation was evident when compared with abdominal irradiation without pelvic boosts and pelvic irradiation alone (5-year disease-free survival rates of 50%, 33%, and 33%).
respectively).

In 1985, the Northwest Oncologic Cooperative Group of Italy embarked on a prospective trial that randomized patients with high-risk early-stage disease (stage IA or IB tumors with poor differentiation, stage IC, and stage II) to chemotherapy (cisplatin, 50 mg/m², plus cyclophosphamide, 600 mg/m², on day 1 every 28 days for six courses) or abdominopelvic irradiation (43.2 Gy to the pelvis and 30.2 Gy to the abdomen) [63]. For the entire series, 5-year survival was 71% and 53% (P = .16), while relapse-free survival was 74% and 50% (P = .07) for the chemotherapy and abdominopelvic irradiation groups, respectively.

Several qualifying statements about this study should be underscored. The trial was prematurely closed secondary to poor accrual and inadequate protocol compliance. Nearly 15% of the patients (9/69) did not have complete surgical staging. The distribution of patients to the respective treatment arms was skewed; chemotherapy was administered to 44 patients, while radiotherapy was administered to only 25. Protocol violations were scored in eight patients randomized to abdominopelvic irradiation, and two patients terminated abdominopelvic irradiation due to life-threatening toxicities. Of note, the higher daily fractional dose of irradiation as administered in this study (1.8 Gy instead of 1.5 Gy) may have contributed to the poor tolerance. Moreover, radiotherapy was delivered with 18 mV photons, which may have underdosed superficially located peritoneal surfaces. Indeed, when the data were analyzed according to treatment received, rather than treatment assigned, no clinically meaningful differences were observed in relapse-free or overall survival at 5 years (73% versus 60% relapse-free survival [P = .3]; 73% vs 68% overall survival [P = .7] among those receiving chemotherapy and irradiation, respectively).

Summary

In summary, the weight of clinical evidence suggests that pelvic irradiation alone has no role in the adjuvant management of optionally debulked early-stage ovarian cancer (Table 6). Among the subgroups of stage I to II disease with significant risks for relapse, eg, grades 2 to 3, dense adherence of the primary tumor to adjacent structures, and greater than 250 cc of ascitic fluid, abdominopelvic irradiation should be used when external beam treatment is considered [15]. Unfortunately, prevailing biases have precluded the completion of randomized trials directly comparing abdominopelvic irradiation with state-of-the-art chemotherapy regimens following adequate cytoreductive surgery for patients with high-risk stage I to II disease. The recent abortive attempt by the Northwest Oncologic Cooperative Group of Italy to mount such a trial emphasizes the difficulties associated with such efforts.

References:


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