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Perspectives and Commentaries

Specialized Surgery in Ovarian Cancer

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(A COMMENT ON: Fiorentino MV, Nicoletto O, Besi PD *et al.* Localized ovarian cancer: Surgery plus chemotherapy. *Eur J Cancer Clin Oncol* 1986, **22**, 1365–1370)

THE ADVANCES in the past decade concerning surgical staging in presumed localized ovarian cancer and debulking surgery in advanced ovarian cancer clearly point out the need for specialized surgery for women with ovarian carcinoma. It can now almost be stated unequivocally that ovarian cancer is "a surgical disease," while multi-drug chemotherapy or whole abdominal radiation are adjuvant modalities.

Only a decade ago, 30–40% of women with Stage I ovarian cancer died of their disease in less than 5 years. Although this survival rate was unacceptably low the reason for failure by hysterectomy and bilateral salpingo-oophorectomy alone, with or without pelvic radiation, was, in many instances not known. We now know through more accurate surgical pathological staging that many such cancers are indeed not localized, but rather have predictable sites of early subclinical or previously unrecognized metastasis. This knowledge allows for a more accurate prediction of patient survival as well as for improved treatment planning, which may, for the first time in 10 years, improve the survival rate for women with early stage ovarian cancer.

A series of studies in the 1970s identified five sanctuaries of occult or subclinical metastases from what was considered at initial surgery to be localized ovarian cancer: (1) diaphragm, (2) omentum, (3) pelvic lymph nodes, (4) para-aortic lymph nodes, and (5) malignant peritoneal cytology. There have been two studies documenting the incidence of such occult or unrecognized metastasis from what appeared to be an ovarian cancer confined to the ovary (Stage I) or to the pelvis (II) [1, 2].

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In the first collective review of the incidence of occult or subclinical metastasis in Stage I and II ovarian carcinoma, Piver and associates found metastasis in the diaphragm 11.3%, aortic lymph nodes in 13.3%, the pelvic lymph nodes in 8.1%, omentum in 3.2%, and malignant peritoneal washings in 33.3% [1]. In women with presumed Stage II ovarian cancer, the sites of metastasis were the diaphragm in 23%, omentum in 0% and peritoneal washings showed malignancy in 12.5%, aortic lymph nodes in 10%.

The United States Ovarian Cancer Study Group (the National Cancer Institute, M.D. Anderson Tumor Institute, the Mayo Clinic, and Roswell Park Memorial Institute) performed a cooperative prospective study to document the incidence of occult or unrecognized metastasis from early staged ovarian cancer [2]. They re-evaluated 100 women with presumed clinical Stage I or II ovarian cancer referred to one of the four member institutions within 4 weeks of initial surgery performed elsewhere. Thirty-one women were reclassified to a more advanced stage with 23% to Stage III by restaging laparatomy and/or other procedures. Clearly, the discovery of Stage III disease in the latter 23% of patients, rather than presumed Stage I or II, allows these women to receive the best treatment for Stage III ovarian cancer.

The results of these two studies clearly explain the failure of surgery alone, or a combination of surgery and pelvic radiation to improve survival in non-surgically staged Stage I or II ovarian cancer. The use of surgical staging in clinically localized Stage I or II ovarian cancer caused a re-evaluation of the proper role of postoperative adjuvant therapy, with the clear possibility of defining a subset of Stage I patients who would not

need adjuvant therapy if careful surgical staging revealed no evidence of disease outside of the ovary.

The Ovarian Cancer Study Group, in conjunction with the Gynecologic Oncology Group, a cooperative group comprising more than 20 United States institutions, was the first to address the issue of the role of adjuvant therapy in patients who underwent formal surgical staging for clinically localized ovarian cancer. In the first of two trials, 56 patients considered to be at low risk for recurrent disease (i.e. stages $I\text{–}A_1$ or $I\text{–}B_1$, well-differentiated or moderately-differentiated tumor with no evidence of metastasis by complete surgical staging) were randomized to no further treatment or melphalan chemotherapy [3]. The survival rate exceeded 90% for the melphalan and observation group, indicating that in this subset of carefully staged patients, the incidence of recurrence is so small that they probably do not need further therapy [4]. Considering the toxicities of multiple drug chemotherapy or whole abdominal radiation, the possible lack of need for such therapy in this subset of patients is of major importance.

The second trial carried out by the Ovarian Cancer Study Group and the Gynecologic Oncology Group included 101 women that were excluded from the above-described trials because they were considered to be at too high a risk for recurrence to be included in a trial arm that has no treatment: Stage $I\text{–}A_{11}$, $I\text{–}B_{11}$, poorly-differentiated, or II–A, II–B, or II–C [3]. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and complete surgical staging, to verify that they had no disease outside the pelvis. Moreover, at the completion of such surgery, they had no residual macroscopic cancer prior to postoperative therapy. Patients were randomized to receive either melphalan or intraperitoneal chromic phosphate (P^{32}) in order to eradicate any possible residual subclinical disease. Median follow-up for surviving patients in this trial was 31 months. However, 2 year disease-free survival was only 81%, a rate probably not indicative of the therapeutic efficacy desired in such carefully staged patients with no residual cancer, and a percentage that will probably decrease as the patients approach the 5-year mark.

Therefore, in the first randomized trial (melphalan vs. observation) in early ovarian cancer in carefully staged patients, it appears that the survival rate will be significantly improved over past rates (90%), and that possibly these patients do not require postoperative adjuvant therapy. In the second randomized trial (melphalan vs. P^{32}), clearly a new form of therapy is required, which is neither melphalan nor intraperitoneal chromic phosphate, but indeed may be multiple drug chemotherapy. Fiorentino and co-authors, in an important study, evaluated the role of adjuvant adriamycin and cyclophosphamide in 37 patients with Stage I and II ovarian cancer [5]. Of the 16 (15 Stage I, one Stage II–A) patients who underwent complete surgical staging plus chemotherapy, the actuarial disease-free survival was 100%. This compared to a disease-free survival of only 77% for the 21 patients (16 Stage I, and five Stage II–A and B) who did not undergo complete surgical staging prior to chemotherapy. The authors concluded that the 100% disease-free survival in the completed staged patients was attributable to the surgical staging plus adriamycin and cyclophosphamide and the poorer results in the incomplete staged patients, was due to the incompleteness of the surgery. An equal argument can be made for the conclusion that the excellent survival was due to the complete surgical staging which selected out a subset of patients who do not require adjuvant chemotherapy. Only a randomized trial of completely staged patients treated by adriamycin and cyclophosphamide (with or without *cis*-platinum) vs. observation would answer this question.

Since 70% of patients with ovarian carcinoma present with Stage III and IV disease, the need for specialized surgery is of obvious importance in this cohort of patients. Many surgeons are often discouraged at the time of laparotomy when confronted with widespread ovarian malignancies. This feeling not infrequently results in biopsy of the most easily accessible tumor nodules (omental biopsy) as the only surgery performed. This conclusion was documented in a review of 100 consecutive patients referred to Roswell Park Memorial Institute for treatment of ovarian carcinoma in 1971 to 1972 [6]: the most common operation was an omental biopsy or abdominal tumor biopsy, which occurred in 34% of the patients. Moreover, no effort at removing as much of the cancer as possible was attempted.

Possibly the most compelling study of the benefit of debulking surgery was that of Griffiths and Fuller who demonstrated that patients with Stage III or IV ovarian cancer with postoperative tumor nodules less than 1.6 cm in greatest diameter, not requiring debulking surgery to achieve that size, had a 40-month survival of approx. 20% [7]. This compared to a similar 30% survival at 40 months for those patients who underwent debulking surgery that resulted in residual tumor similarly less than 1.6cm in diameter. By sharp contrast, however, no patient survived 40 months with residual disease greater than 1.5 cm. Therefore, it appears that it was not the percentage of the tumor removed or the volume of the tumor present initially, but the volume of the residual tumor

after debulking surgery that was significant for improved survival.

This increased survival was clearly pointed out in the long-term study of Wharton *et al.* of 395 women with Stage III and IV ovarian carcinoma treated with chemotherapy; 40% of the patients with residual cancer ≤ 2 cm survived 4 years, compared to only 14% of patients with residual cancer > 2 cm ($P = 0.001$) [8]. Even with this information that improved survival of patients with advanced ovarian cancer which primarily depended on having small residual disease prior to chemotherapy, a recent 1985 report comparing *cis*-platinum, adriamycin and cyclophosphamide to chlorambucil, 71% of the *cis*-platinum, adriamycin and cyclophosphamide patients and 80% of the chlorambucil patients were entered into the trial with residual disease > 2 cm. Retrospectively, the fact that survival rates were not better for the combination chemotherapy patients, as compared to chlorambucil could have been predicted at the onset of the study [9].

In order to evaluate what percentage of women in Stage III and IV ovarian carcinoma could have their tumors adequately debulked (≤ 2 cm), we performed a prospective study on 50 consecutive patients referred to Roswell Park Memorial Institute with Stage III and IV ovarian cancer. One hundred percent of the women underwent bilateral salpingo-oophorectomy, 98% hysterectomy, 86% omental resection, 36% intestinal resection, and 16% resection of the gastrocolic ligament [10]. Of the 50 patients, 76% had their tumors debulked to ≤ 2 cm. Of these 50 patients, 18 had been previously operated on within the previous 3–4 weeks, and were considered inoperable. In this group, all 18 underwent immediate reoperation at Roswell Park Memorial Institute and 77% could have their tumors adequately debulked to ≤ 2 cm. Of major concern from such aggressive surgery was the degree of postoperative morbidity and possible mortality and delay in initiation of chemotherapy. Of the 50 patients, 58% (29) had no complications, and there were no postoperative deaths. Chemotherapy was started in less than 2 weeks in 92% of the patients.

In summary, it is clear that ovarian cancer is primarily a "surgical disease," and that in clinically localized ovarian cancer, careful surgical staging may spare a subset of patients adjuvant therapy. For those patients that had microscopic metatasis discovered at surgical staging, they will be afforded the best therapy for Stage III ovarian cancer. Finally, for patients with advanced Stage III or IV disease, improved survival will only result by aggressive debulking surgery followed by the best adjuvant therapy.

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