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Surgery in ovarian cancer

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Summary

The role of surgery in the management of primary and recurrent ovarian cancer is reviewed. The data to support primary and secondary cytoreduction are summarized. The role of second-look surgery and of surgery in the palliation of ovarian cancer is also discussed.

Key words: Primary cytoreduction; Neoadjuvant chemotherapy; Secondary cytoreduction; Second-look laparotomy.

Introduction

Surgery plays a crucial role in the management of epithelial ovarian cancer. Survival in ovarian cancer is influenced by many factors, including age, performance status, stage, grade, ploidy, volume of disease at presentation, volume of disease at completion of cytoreduction, and chemosensitivity. These factors contribute to the "biology of the tumor." Other factors that contribute to the biology of ovarian cancer include host immune status and the inherent unfavorable characteristics of large masses in terms of responsiveness to therapy, including poor perfusion, decreased delivery of chemotherapeutic agents, more cells in G0, and higher likelihood of resistant clones. The only prognostic factor that the gynecologic surgeon can truly influence is the amount of residual disease remaining at the completion of the primary debulking operation. The importance of the gynecologic surgeon's ability to achieve optimal cytoreduction of ovarian cancer cannot be overemphasized because of its impact on survival. Additional benefits of cytoreduction include relief of symptoms, reduction of ascites, decrease in abdominal distention, improvement in intestinal function, and improvement in nutritional status. Surgery also plays an important role in the management of recurrent and progressive disease.

Primary cytoreduction is defined as cytoreductive surgery before the initiation of chemotherapy, either as an initial operation or as a secondary attempt by another surgeon after a suboptimal procedure. Secondary cytoreduction is debulking surgery after chemotherapy, whether performed as an interval procedure, as part of a second-look operation, or as part of the management of progressive or recurrent disease. This article provides an overview of the role of primary and secondary cytoreductive surgery in the management of ovarian cancer.

Primary Cytoreduction

As defined above, primary cytoreduction is employed before the initiation of chemotherapy, either as an initial operation or after previous suboptimal debulking. Optimal cytoreduction is variously defined as reduction of the largest residual tumor nodule to no larger than 1.5, 1.0, or 0.5 cm or even as no visible residual disease. This radical surgical approach has been shown to be feasible, safe, and of benefit to the patient. Most importantly, it is the only factor under the control of the surgeon which has an impact on patient outcome.

The feasibility of cytoreduction with acceptable morbidity has been well documented. Heintz *et al.*[1] reported that optimal cytoreduction was achievable in 56.4% of patients, which improved to 87.1% with increased operator experience. Serious morbidity occurred in 23.7% and included pneumonia, wound dehiscence, cardiac failure, and bleeding requiring reexploration. Mortality was 2.9%. Bowel surgery was performed in 22.5% of patients in the optimal group. Eisenkop *et al.* [2] achieved optimal cytoreduction in 98.8% of women in a consecutive series, with a perioperative mortality of 1.8%.

Optimal cytoreduction results in improved survival. Hoskins [3] reviewed the effect of primary cytoreduction in women with ovarian cancer and found that in 388 patients who had optimal cytoreduction, median survival was 36.7 months as compared with 16.6 months for 537 patients with suboptimal procedures. Additionally, optimal cytoreduction also improved progression-free survival, with a median value of 33.5 months for 200 optimally debulked patients as compared with 15.0 months for 374 women with suboptimal cytoreduction. Survival time has been correlated to maximal residual abdominal tumor diameter, with a statistically significant difference for < 1cm as compared with > 1cm ($p = 0.0017$) and for 1 to 2 cm as compared with > 2 cm ($p < 0.01$) [4, 5]. Therefore, the goal of cytoreduction should be removal of all gross residual disease or at least cytoreduction to less than 1 cm.

Effective cytoreduction, however, clearly also depends on the type of practitioner performing the surgery. In the National Survey of Ovarian Carcinoma, significantly different patterns of care were noted [6, 7]. Cytoreductive surgery was performed by a gynecologic oncologist in 20.8% of cases in this series, by a gynecologist in 45%, and by a general surgeon in 21.1%. Optimal cytoreduction was achieved in 42%-45% of cases performed by a gynecologic oncologist, 40%-44% of those performed by a gynecologist, but only 25% of those performed by a general surgeon. Gynecologic oncologists were also more likely to perform a hysterectomy, omentectomy, lymphadenectomy, and peritoneal biopsies than other practitioners. Additionally, general surgeons were more likely to perform colostomies. This difference among practitioners in achieving optimal cytoreduction translates into a survival difference: patients cared for by general surgeons had a significantly reduced survival ($p < 0.004$). In a review of patterns of care in the United States, Munoz *et al.* [8] reported that only 9% of stage I patients received "state of the art" care, as defined by the NIH Consensus Conference as complete surgical staging, while 71% of stage III and 53% of stage IV patients underwent complete staging. The majority of stage I patients did not receive "state of the art" care because lymphadenectomy was lacking at the time of staging.

Cytoreduction may encompass more than a simple hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Operability does not depend on the extent of pelvic disease but on the extent of upper abdominal and extra-abdominal disease. To facilitate resection of the pelvic disease, the retroperitoneal approach should be employed when there is extensive disease in the pelvis. This approach involves removing en bloc the bladder peritoneum, pelvic sidewall peritoneum, cul de sac peritoneum, uterus, tubes and ovaries, and the rectosigmoid as well, if indicated. Pelvic lymphadenectomy is also included. This approach may be aided by positioning the patient in the synchronous or "ski" position to facilitate use of the intraluminal stapler, because the need for bowel resection can be difficult to predict preoperatively. In a personal series, Webb [9] achieved optimal cytoreduction in 70.8% of 208 consecutive patients with the use of these principles. Reasons for suboptimal debulking included a fixed pelvic mass in only one patient, extra-abdominal disease in ten patients, and unresectable upper abdominal disease in 45 patients. This approach has been duplicated by other groups, with similar feasibility and success [10, 11].

Bowel resection may be necessary to achieve optimal cytoreduction. It may be performed to achieve debulking or to prevent or treat obstruction. Over a 10-year period at the Mayo Clinic, 180 patients underwent bowel resection as part of a primary debulking operation [12]. The number of resections varied: 115 patients had a single bowel resection, 25 patients had two resections, and 4 had three. Small bowel resection was performed in 64 patients, right hemicolectomy in 13, transverse colectomy in 14, and rectosigmoid resection in 117. Debulking was the primary indication for bowel resection in 87%, and residual disease was microscopic in 15%, < 0.5 cm in 27%, 0.6-1.5 cm in 21%, and > 1.5 cm in 37% of patients. The benefits of bowel resection in achieving optimal cytoreduction, particularly in terms of survival, outweigh the morbidity associated with the surgery [13].

The ability to achieve optimal cytoreduction is thus dependent on the volume of upper abdominal disease. Disease may be encountered in the omentum, liver, spleen, and/or diaphragm. Omental disease is best approached with a complete omentectomy rather than a subtotal omentectomy and is usually accomplished without risk to the colon. Rarely, resection of the transverse colon may also be required for complete removal of the tumor.

Upper abdominal disease involving the liver or spleen may affect the surface or the parenchyma. Liver resection can be employed to resect surface lesions or parenchymal metastases. In stage IV disease, liver resection performed to achieve optimal cytoreduction is feasible and improves overall survival. In a series of 84 women with stage IV disease, median survival was 50.1 months in patients with optimal cytoreduction, as compared with 25.0 months in patients who had optimal abdominal cytoreduction but had residual disease in the liver of > 1 cm ($p < 0.0001$) [14]. Twenty-four patients who underwent liver resection for metachronous parenchymal liver metastasis between 1976 and 1999 at the Mayo Clinic had a median postoperative survival of 14.1 months (range 5.0-41.3 months). Twenty patients achieved optimal cytoreduction, as defined as extrahepatic and hepatic residual disease < 1 cm. Postoperative complications occurred in 20.8%, and there was no postoperative mortality [15]. Splenic disease can be addressed by using the CUSA ultrasonic scalpel, the argon beam coagulator, or splenectomy [16, 17]. In a review of splenectomies done in the course of ovarian cancer cytoreduction at the Mayo Clinic between 1983 and 1992, 50 splenectomies were performed - 27 at the time of primary operation and 23 at the time of second-look (Silverman MB, Adams PB, Jacobsen SJ, *et al.*, read at 25th Annual Meeting of the Society of Gynecologic Surgeons, San Diego, 1999). Metastatic involvement necessitated removal in 54%, en bloc resection was performed in 32%, and intraoperative trauma required removal in 14%. Major complications were seen in 28%, and there were three postoperative deaths. In a series of 35 splenectomies performed for cytoreduction, optimal cytoreduction (< 1 cm) was achieved in all primary patients, with 23.1% major morbidity, and in 86% of secondary patients, with 28.6% major morbidity [17]. Hence, liver resection and splenectomy are reasonable adjunct procedures in trying to achieve optimal cytoreduction.

Diaphragmatic disease is best approached by division of the hepatic and falciform ligaments to improve exposure. Cytoreduction can then be accomplished by using the CUSA ultrasonic scalpel or the argon beam coagulator, excising the peritoneum over the diaphragm, or resecting a segment of the diaphragm.

Pelvic and para-aortic lymphadenectomy at the time of primary cytoreduction is important for staging purposes and may also play an important therapeutic role. In a case-control study of lymphadenectomy in advanced ovarian cancer, Scarabelli *et al.* [18] demonstrated a survival benefit in previously untreated patients subjected to lymphadenectomy as compared with patients who did not undergo lymphadenectomy, with a 2-year survival of 59% versus 16% ($p < 0.001$). In a retrospective analysis of 488 women with advanced ovarian cancer, multivariate analysis showed a significant impact of lymph node status on 5-year survival [19]. Cytoreduction of grossly involved nodes can also be performed in order to achieve optimal results.

In known stage IV disease, cytoreduction may still be justified. Boente *et al.* [20] reported on a cumulative series of 266 women with stage IV disease and noted a survival difference based on cytoreductive status - 109 patients with optimal cytoreduction had a median survival of 33 months (range 25-40 months) and 157 with suboptimal results had a median survival of 17 months (range 15-22 months). Bristow *et al.* [14] also showed a survival benefit of aggressive cytoreduction, including liver resection, in 84 women with stage IV disease. However, in patients with extensive liver, retroperitoneal, or upper abdominal disease by computed tomography scan or in those who are medically unfit to undergo extensive cytoreduction, neoadjuvant chemotherapy can be considered, followed by interval debulking if there is measurable clinical response.

Neoadjuvant chemotherapy has been promoted for patients with large-volume disease or poor performance status. Optimal cytoreduction was achieved in 79% of 43 patients treated with two cycles of neoadjuvant chemotherapy [21]. Park (read at 33rd Annual Meeting of the American Society of Clinical Oncologists, 1997) presented a similar series of patients, considered unsuitable for surgery by computed tomography or magnetic resonance imaging, who underwent neoadjuvant chemotherapy. The overall response rate for 15 stage III and four stage IV patients treated with six cycles (mean 4.1) of CAP chemotherapy was 78.9%, and 18 of the 19 had optimal cytoreduction. There was no residual disease at the time of cytoreductive surgery in 22.2%. Schwartz *et al.* [22] reported on the long-term survival of 59 women with advanced ovarian cancer treated with neoadjuvant chemotherapy. Patients receiving chemotherapy were slightly older than their control cohort of 206 stage III and IV patients who underwent initial cytoreduction - 67 versus 60 years - and had a poorer Eastern Cooperative Oncology Group (ECOG) performance status. However, there was no statistical difference in progression-free survival or overall survival between the two groups, although the median survival was 1.07 and 2.18 years, respectively. Women who did undergo cytoreductive surgery after neoadjuvant chemotherapy had a statistically improved survival ($p < 0.0001$) and, in a previous series from the same group [23], there were no long-term survivors among patients who received neoadjuvant chemotherapy but did not undergo subsequent cytoreduction. Therefore, neoadjuvant chemotherapy is a reasonable approach in patients for whom cytoreduction is initially deemed inappropriate, but for long-term benefit it should be followed by cytoreductive surgery in those patients who respond.

Secondary Cytoreduction

As previously defined, secondary cytoreduction is debulking surgery performed after chemotherapy when there had been a previous primary operation. It may be performed as an interval step halfway through planned treatment with chemotherapy in patients who could not be optimally debulked at primary operation (interval cytoreduction), at the time of second-look surgery, or after recurrence.

Interval Cytoreduction

The rationale for interval surgery after chemotherapy is that debulking is confined to patients who have responded and that, with a smaller volume of disease, the ability to effectively debulk the tumor is increased. Interval cytoreduction was effective in achieving optimal cytoreduction in 64% of a cohort of 278 patients [24]. Reported rates of optimal cytoreduction at the time of interval cytoreduction range from 8% to 96% [25]. The difficulty with interval cytoreduction is in the assessment of results. In trying to define what percent of patients were truly inoperable based on the pattern of disease spread at the time of first surgery, it is necessary to take into consideration the skill or type of training of the operating physician. In addition, the variations in tumor biology and the impact of the delay in cytoreduction on survival are not known, and survival comparisons are difficult in patients who never undergo cytoreduction. This question is currently being studied prospectively by the Gynecologic Oncology Group (GOG), but mature data are not yet available.

Second-look Laparotomy

Second-look laparotomy provides a secondary assessment of the responsiveness of the disease to chemotherapy. Surgical morbidity in second-look surgery is similar to that of primary cytoreductive surgery [26]. In patients who achieve a clinical complete response to standard chemotherapy, approximately 50% still have active malignancy at the time of subsequent surgical evaluation. Over a 9-year period at the Mayo Clinic, 250 women underwent second-look laparotomy and 46% were found to be positive, with disease of ≥ 1 cm in 39 patients [27]. Second-look findings correlate with findings at the completion of primary debulking. In one series, 34% of patients who had had microscopic residual disease at the completion of primary debulking were positive for disease at second-look, compared with 64% who had had residual disease of < 2 cm, and 91% who had had suboptimal cytoreduction [28]. Unfortunately, women with advanced-stage disease initially, who are negative for disease at second-look, are still at appreciable risk of subsequent relapse - recurrence-free survival in 44% at 5 years and 40% at 10 years in one series and there is a 30% relapse rate in another [29, 30]. The benefit of second-look laparotomy is controversial, although it does provide an unrefutable assessment of the effectiveness of primary therapy.

Patients with macroscopic disease at the time of second-look may benefit from secondary cytoreduction. Secondary cytoreduction at the time of second-look is not only feasible but may also provide a survival advantage. Hoskins *et al.* [31] reported on 67 patients who underwent secondary cytoreduction at the time of second-look. Reduction to microscopic residual disease was achieved in 23.9%, and optimal debulking was possible in an additional 38.8%. The 5-year survival for the 17 women who had only microscopic disease at the time of second-look was 62%, and it was 51% for the 16 women whose disease was reduced to a microscopic level at the completion of second-look; this difference was not statistically significant. For the 32 women with macroscopic residual disease at the completion of the procedure, 5-year survival was only 10%. Podratz *et al.* [27], also reporting on survival rates after secondary cytoreduction at the time of second-look surgery, found that 4-year survival rates were statistically significantly related to volume of residual disease at the completion of the procedure - 55% for microscopic residual, 21% for disease < 5 mm, and 14% for disease > 5 mm ($p < 0.01$). Williams *et al.* [32] reported the results of a GOG study that showed a reduction in relative risk of death to 0.48 in patients debulked from ≤ 1 cm to microscopic disease, 0.49 for > 1 cm reduced to ≤ 1 cm, and 0.44 when cytoreduction was to microscopic disease. If not performed at the time of initial surgery, pelvic and para-aortic lymphadenectomy should be performed at the time of second-look surgery because 17.7% of patients may have residual nodal disease in the absence and 63.6% in the presence of intra-abdominal disease [33]. Despite the appreciable risk of recurrence after a negative second-look laparotomy, the survival benefit afforded patients whose disease is optimally debulked at the time of second-look laparotomy supports the continued use of this procedure.

Surgery in Recurrent Disease

Unfortunately, even women with negative second-look operations are at risk for recurrent disease. In a series of 50 advanced-stage ovarian cancer patients who had negative second-look operations, 15 (30%) had recurrence. Patients over age 67 who have residual tumor of more than 2 cm after primary cytoreductive surgery and a higher histologic grade were more likely to experience recurrence [30]. Surgery in recurrent disease can be either therapeutic or palliative. For surgery with therapeutic intent, secondary cytoreduction can provide a survival advantage as well as relief from symptoms. Secondary cytoreduction is best employed for patients who have a low-grade tumor, an initial response to chemotherapy, and a reasonable disease-free interval. There should be no ascites, and effective postoperative adjuvant therapy should be available. Cytoreduction should only be undertaken if optimal debulking is feasible. Success rates for optimal cytoreduction in persistent or recurrent disease are 50% to 60%, with total complication rates of up to 35% [34]. Although the need for a bowel resection to achieve optimal cytoreduction in the course of secondary debulking has reportedly had a negative impact on survival, other series have refuted this finding [35]. If optimal cytoreduction is otherwise feasible, splenectomy and liver resection may also be employed as part of secondary cytoreduction [15, 36] (Silverman M. B., Adams P. B., Jacobson S. J. *et al.*, read at 25th Annual Meeting of the Society of Gynecologic Surgeons, San Diego, 1999).

Secondary cytoreduction should not be used for patients who do not respond to initial therapy or for those in whom recurrence develops rapidly after primary therapy. Nor should surgery be employed for therapeutic purposes in patients with progressive disease while on therapy, because it is of no benefit. Michel *et al.* [37] reported on 77 patients who underwent secondary cytoreduction for progressive disease. Median survival was the same, 12 months, for 32 patients who underwent optimal debulking (< 2 cm residual disease) and for 45 women whose disease was suboptimally debulked. Morris *et al.* [38] reported similar findings on secondary cytoreduction in women who did not respond to first-line therapy. Bowel resection was required in 66% of the 18 women to achieve optimal (< 2 cm) cytoreduction. Median survival was 9.4 months. For patients with residual disease of < 1 cm, median survival was 19.5 months, compared with 8.3 months for those with residual disease of > 1 cm ($p = 0.004$). For women with a disease-free interval of less than 12 months, median survival was 7.3 months, whereas it was 18.3 months for those who had been without evidence of disease for more than 12 months ($p < 0.004$). In the series of Berek *et al.* [39], patients with ascites had a median survival of five months as compared with 18 months for those who did not ($p < 0.01$). Kuhn *et al.* [40] also reported on the poor outcome in women with rapid recurrence after primary therapy, with a median survival of 15 months. Therefore, for patients with poor prognostic factors such as rapid relapse after primary therapy, nonresponsiveness to primary therapy, or ascites, secondary cytoreduction is not indicated.

However, in properly selected patients, secondary cytoreduction can extend median survival. In the series of Berek *et al.* [39], for the 38% of patients who underwent secondary cytoreduction and had optimal debulking (< 1.5 cm), median survival was 20 months, compared with five months in the suboptimal group. Segna *et al.* [35] reported a survival benefit ($p = 0.0001$) in 61 patients who underwent optimal secondary cytoreduction after recurrence or progression following cisplatin-based chemotherapy, compared with 39 patients with suboptimal cytoreduction, median survival having been 27.1 months and nine months, respectively. Not only can secondary cytoreduction provide a benefit in terms of median survival but it can also afford improvement in or resolution of the patient's symptoms [41].

Salvage chemotherapy does not provide a similar survival benefit compared with secondary cytoreduction, and it may have a negative impact on the outcome of secondary surgery. Kuhn *et al.* [40] prospectively studied secondary cytoreduction compared with second-line chemotherapy in patients who had recurrence more than 12 months after completing initial chemotherapy. They noted a statistically significant advantage for women treated with multi-modality therapy. Median survival for the 59 patients treated with secondary cytoreduction followed by chemotherapy was 38 months, while that for the 37 women treated with chemotherapy alone was 12 months ($p < 0.0001$). Salvage chemotherapy may also have a negative impact on the ability to achieve optimal secondary cytoreduction. In a series of 106 women with a disease-free interval of > 6 months who underwent secondary cytoreduction [42], multivariate analysis revealed that the use of salvage chemotherapy before secondary cytoreduction was a significant negative predictor of survival, with median survival of 24.9 months for patients treated initially with salvage chemotherapy and 48.4 months for those who were not. Thus, in properly selected patients, secondary cytoreduction can provide benefit.

Surgery in Palliation of Ovarian Cancer

For women whose disease progression and resistance to chemotherapy precludes therapeutic surgery, surgery may be employed for palliation of symptoms. Gastrostomy tubes provide decompression of intestinal obstruction and permit continued limited oral intake. Although preferably done in the endoscopy suite, g-tube placement sometimes requires a limited operative procedure because of an appreciable volume of upper abdominal disease. Palliative surgery for bowel obstruction may include bowel resection or colostomy. However, because of the significant risk of enterocutaneous fistula and anastomotic leak in patients with active malignancy who undergo multiple operations, this represents a very small and highly selected population, best determined on a case-by-case basis.

Conclusions

Used judiciously, surgery can offer women with ovarian cancer relief from symptoms, but more importantly, it can provide survival benefits at the time of initial diagnosis, second-look laparotomy, and secondary cytoreduction of recurrent disease. Surgeons involved in the care of these women must continue to strive to achieve optimal cytoreduction whenever possible. This may be facilitated through the retroperitoneal approach to bulky pelvic disease and also through aggressive surgical cytoreduction, including lymphadenectomy, bowel resection, splenectomy, and liver resection. If the examining physician does not have the appropriate training to perform these procedures, it is important that the patient be referred to someone who does.

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