Cytoreductive Surgery in Ovarian Cancer: Why, When, and How?

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Retrospective evidence supports the value of optimal cytoreductive surgery in the initial therapy of patients with advanced ovarian cancer. Specialized procedures, including radical pelvic surgery, bowel resection, and diaphragm resections, are frequently necessary to accomplish optimal cytoreduction. Cytoreduction and total gross tumor removal are possible more frequently with new surgical instruments such as the Cavitron ultrasonic surgical aspirator and argon beam laser. Pelvic and periaortic lymph node resection is an important aspect of cytoreductive surgery, and systematic removal of grossly uninvolved lymph nodes may improve survival. Secondary cytoreductive surgery appears to benefit a select group of patients.

Introduction

Ovarian cancer is an insidious disease and the fourth leading cause of cancer deaths in women in the United States. The majority of women who contract this disease will die as a result, mostly due to uncontrolled, large-volume disease within the peritoneal cavity. More than 70% of women are initially diagnosed with disseminated intraperitoneal disease. Generally, ovarian cancer is surgically diagnosed. In addition to diagnosis, two other classic aims of ovarian cancer surgery are the appropriate determination of extent of disease (staging) and the removal of as much tumor as is feasible (debulking or cytoreduction) to maximize postoperative therapy. This discussion focuses on issues regarding debulking surgery in both primary and subsequent therapy.

Ovarian cancer metastasizes by breaking through the ovarian capsule and spreading noncontiguously along parietal and visceral peritoneal surfaces. It tends not to invade deeply or into hollow organs, and in most patients the disease remains confined to the peritoneal cavity until death. The disease may become focally confluent and can form large-volume masses anywhere in the peritoneal cavity. Typical locations include the omentum, sigmoid colon serosa, and pericolic gutters. Patients become symptomatic usually as a result of intraperitoneal pressure increases due to solid masses or fluid. Some patients are asymptomatic in spite of surprisingly large volumes of intraperitoneal disease. The regional lymph nodes, namely pelvic and periaortic lymph nodes, are frequently involved. This is particularly true in stage III and IV disease in which Burghardt et al[1] reported involvement in 74% of patients.

Because ovarian cancer metastasizes usually are relatively superficial, the disease lends itself technically to cytoreductive surgery often without major organ resection. The question arises as to the benefit of this surgery to the patient. In theory, benefits could include symptomatic relief, prolongation of survival even without further therapy, and enhancement of postoperative therapy in terms of both survival duration and chance for cure. All of these apply to ovarian cancer debulking surgery.

Primary Cytoreductive Surgery

The initial study suggesting that cytoreductive surgery is of value in the primary therapy of ovarian cancer was published in 1975.[2] In this study, patients who were cytoreduced to a maximum residual diameter of 1.5 cm or less survived as well as patients with residual disease of 1.5 cm or less without cytoreduction. Survival of these two groups was markedly superior to patients with maximum residual disease greater than 1.5 cm in diameter. Since this initial study, multiple retrospective studies have demonstrated superior survival in patients whose residual disease was 1 to 3 cm in maximum diameter compared with patients with larger residual masses.[3-10] In summarizing these studies, Hoskins[11] noted a median survival of 36.7 months in 388 patients who were optimally cytoreduced vs 16.6 months in 537 patients with suboptimal residual disease.

These studies demonstrate that the size of residual disease has a profound impact on survival. However, they do not prove unequivocally that cytoreductive surgery resulting in small residual disease is responsible for the improved survival in these patients. A large randomized, prospective study would be necessary to demonstrate this, and to date this has not been done. Because of the large volume of retrospective evidence suggesting that cytoreductive surgery is beneficial in the primary therapy of ovarian cancer, most physicians treating these patients believe in its value. As a result, it is very likely that a prospective, randomized study will never be done, even in a cooperative group setting. Given these circumstances, cytoreductive surgery is firmly entrenched in the initial management of ovarian cancer patients.

While Griffiths' initial study[2] suggested that patients with large volume metastatic disease who were cytoreduced to small volume residual disease did as well as patients with small volume metastatic disease, this result is not supported in subsequent studies. The initial size of metastatic deposits did impact on survival in patients who were optimally cytoreduced in a study by Hacker et al[3] in 1983. The survival curves in this study are shown in Fig 1. Optimally cytoreduced patients with initial metastatic disease between 1.5 and 10 cm did better than optimally cytoreduced patients with initial metastatic disease greater than 10 cm, but they did worse than patients with initial metastatic disease less than 1.5 cm. In a more recent Gynecologic Oncology Group study[12] involving a much larger number of patients, an identical result was reported. Patients with microscopic upper abdominal metastatic disease survived significantly longer than patients with grossly evident disease less than 1 cm. In turn, the latter group survived significantly longer than patients with upper abdominal metastatic disease greater than 1 cm in diameter who were cytoreduced to less than 1 cm. Tumor biology cannot be completely negated with aggressive cytoreductive surgery. Given equal size of residual disease, patients with larger volume initial metastatic disease will survive less well.

Along similar lines, the number of metastatic lesions affects survival despite optimal cytoreductive surgery. Farias-Eisner et al[13] reported on 78 patients who were cytoreduced to 5 mm or less as the maximum tumor diameter. Patients with scattered residual nodules survived significantly better than patients with extensive carcinomatosis. More specifically, Hoskins and colleagues[12] noted that 20 or more residual lesions resulted in a significantly poorer survival in patients optimally

Pierre Auguste Renoir (French, 1841-1919), Moulin Galette, 1876.
Optimal Residual Disease

The term optimal cytoreductive surgery refers to the maximum diameter of residual disease. The size in various papers has arbitrarily been set anywhere from 5 mm to 3 cm. Optimal cytoreduction may represent a threshold below which survival no longer improves or above which survival no longer improves. The Gynecologic Oncology Group has demonstrated that survival for patients with advanced ovarian cancer progressively decreases as the maximum residual disease increases from microscopic to 2 cm (Fig 2).[14] which demonstrates that optimal survival occurs when there is no gross residual disease. In the same paper, the upper threshold after which survival no longer improves was demonstrated to be 2 cm (Fig 3). Patients with 3-cm residual disease do not survive longer than patients with 10-cm residual disease.

This is particularly useful information for the surgeon who operates on ovarian cancer patients. Every reasonable effort should be made to remove all gross tumor. If that cannot be accomplished, then 1 cm is better than 2 cm of residual disease. If a maximum residual disease of 2 cm or less is not possible, then aggressive surgery such as bowel resection is not appropriate, since survival is not improved.

The percentage of patients with advanced ovarian cancer who are optimally cytoreduced depends on the aggressiveness, patience, and training of the initial surgeon. Taken as a whole, only 42% of the 925 patients in the nine retrospective studies summarized by Hoskins et al[11] were optimally cytoreduced. However, in the most contemporary of the above series reported in 1988,[10] 87% of patients were cytoreduced to less than 2 cm of residual disease. In a retrospective study[15] comparing gynecologic oncologists with nongynecologic oncologists as the initial surgeon, 82% of stage IIIIC or IV ovarian cancer patients were optimally cytoreduced by gynecologic oncologists compared with 29% for nongynecologic oncologists. Most importantly, survival was significantly better in patients cytoreduced by gynecologic oncologists. The surgery done by the gynecologic oncologists was more aggressive since it was associated with a significantly higher operative time, estimated blood loss, hospital stay, need for transfusion, incidence of intestinal resection, and incidence of adynamic ileus. Operative mortality, however, was actually significantly less for the gynecologic oncologists.

Specialized Procedures

Many patients with advanced ovarian cancer can be optimally cytoreduced with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. However, many patients require specialized procedures to achieve this goal. Radical pelvic surgery often is required in patients with large confluent pelvic disease. This radical pelvic surgery frequently requires resection of the pelvic peritoneum, cardinal ligaments, uterosacral ligaments, portions of the sigmoid colon and rectum, and portions of the lower urinary tract. This type of surgery is variously known as radical oophorectomy, modified posterior exenteration, and reverse hysterocolposigmoidectomy.[16-18] The common element is retroperitoneal mobilization of the pelvic disease with en bloc resection.

Resection of a portion of the lower urinary tract is the rarest component of this radical pelvic surgery, and total resection of the bladder with urinary diversion is rarely necessary or justified. However, partial resection of the bladder or ureter to achieve optimal cytoreduction is appropriate. In a series by Berek and colleagues[19] of 24 patients treated in this manner over a 19-year period at University of California at Los Angeles Medical Center, eight patients had partial cystectomies, and 16 had partial ureteral resection. Morbidity was acceptable, and survival was significantly longer for those patients who were successfully optimally cytoreduced compared with those who were not.

Resection of a portion of the sigmoid colon and/or rectum is a frequent component of radical pelvic surgery in advanced ovarian cancer. As a result of modern stapling devices, most of these patients do not require colostomies. In a series by Soper et al[20] of 40 patients, only 12 required colostomy. Serious morbidity and mortality are acceptable with these procedures but are not trivial. Postoperative mortality occurred in two of 117 patients in three combined recent series.[17,18,20] Serious postoperative morbidity ranged from 20% to 39% including wound infection, pulmonary embolus, pelvic abscess, prolonged ileus, and postoperative hemorrhage.

Specialized procedures for optimal ovarian cancer cytoreduction also are frequently necessary in the upper abdomen. This most often involves small bowel resection or resection of colon proximal to the sigmoid colon. Other procedures include splenectomy, resection of diaphragmatic peritoneum, nephrectomy, cholecystectomy, and partial resection of organs such as the liver, pancreas, and stomach. Little is published regarding these specialized procedures. Sonnendecker et al[21] reported six patients out of a total of 79 (7%) with advanced ovarian cancer who underwent splenectomy as part of their primary cytoreductive surgery. Four of these patients had significant late thromboembolic complications with one death. Three of these patients were alive without evidence of disease with a maximum follow-up of 32 months. In another report[22] of 14 patients who underwent diaphragmatic resections, optimal cytoreduction was achieved in 13 patients, and in one patient the procedure was abandoned due to laceration of the liver capsule. Other than the liver capsule injury, there was no other serious morbidity.

Retroperitoneal Cytoreduction

As previously mentioned, pelvic and periarteric lymph nodes are frequently involved in patients with advanced ovarian cancer. The retroperitoneal space as well as the intraperitoneal space, therefore, must be considered in any cytoreductive strategy, and grossly involved lymph nodes should be removed if feasible to achieve optimal cytoreduction. A study[23] published in 1986 addressed the question of the role of the lymph node resection if they are not grossly involved. Seventy patients with stage III ovarian cancer underwent standard intraperitoneal cytoreduction and systematic pelvic and periarteric lymphadenectomy starting at the level of the renal vessels. These patients were compared to 40 similar patients who underwent only intraperitoneal cytoreduction without lymphadenectomy. The actuarial five-year survival was 53% in the lymphadenectomy group and 13% in the nonlymphadenectomy group. In the lymphadenectomy group, those with negative lymph nodes had a
survival rate of 74.7%, and those patients with positive lymph nodes had a survival rate of 45.9%. A Japanese study\[24\] published in 1993 showed similar results in 25 patients with stage III ovarian cancer. A statistically significant survival advantage was shown for 15 patients who underwent lymphadenectomy compared with 10 patients who did not. These studies suggest that systematic pelvic and periaortic lymphadenectomy improves survival in patients with advanced ovarian cancer when combined with optimal intraoperative cytoreduction. A prospective, randomized study is needed to determine if this outcome is a true effect or the result of selection bias.

Systematic pelvic and periaortic lymphadenectomy generally is not part of cytoreductive surgery in the United States. The only report\[25\] in the American medical literature described systematic pelvic and periaortic lymphadenectomy in 56 patients with stage III and IV ovarian cancer. In 21 additional patients, either the procedure was technically not possible or the patient could not be optimally cytoreduced intraoperatively. Positive lymph nodes were present in 64% of patients, and within this group, 64% had macroscopically positive nodes and 36% had microscopically positive nodes. Survival was comparable in patients with negative, microscopically positive, and macroscopically positive lymph nodes (43% to 50%). No major morbidity could be attributed to the lymphadenectomy.

Systematic lymphadenectomy is feasible in most patients with advanced ovarian cancer. Since its employment may have a profound effect on survival, it is worthy of a prospective, randomized study in a cooperative group setting.

### Specialized Instruments

When aggressively pursued, cytoreductive surgery is challenging and often associated with serious morbidity. As a result, there has been interest in the development of techniques such as the Cavitron ultrasonic surgical aspirator (CUSA) that allow more precise tumor removal that may obviate the need for major organ removal. The CUSA fractures the tumor with high-intensity sound energy and removes it with suction while sparing vessels and hollow organ walls. It can be used safely in relatively inaccessible areas. Two initial reports describing its use in ovarian cancer were published in 1988. Adelson et al\[26\] noted no organ resections in 10 patients with a mean CUSA operating time of 49 minutes. A similar experience was noted by Deppe et al\[27\] although they noted that the value of the CUSA was limited in patients with relatively fibrotic tumors. In a later report\[28\] the CUSA was used in 22 of 45 advanced ovarian cancer patients to effect optimal cytoreductive surgery. Sites where the CUSA was used included colon, diaphragm, gallbladder, spleen, stomach, small bowel, and fixed retroperitoneal lymphadenopathy. The report noted only one patient with a fibrotic tumor in which the CUSA was not effective.

Several other techniques have been used to compliment standard surgical techniques in ovarian cancer cytoreductive surgery. Brand and Pearlman\[29\] reported the use of the argon beam laser in this setting with particular emphasis on diaphragmatic lesions as well as bowel serosa and mesenteric lesions. The advantages of this instrument include minimal thermal damage beyond what can be seen and clearance of blood and debris away from the operative site. Other modalities used in this same setting include the carbon dioxide laser and the loop electrosurgical excision procedure.[30,31]

One advantage of the CUSA and argon beam laser is more expeditious removal of widespread, small peritoneal implants. As stated earlier, widespread peritoneal implants in optimally cytoreduced patients are associated with a survival disadvantage. A strategy to overcome this would be the systematic removal of these implants. Eisenkop et al\[32\] reported a case-control study in which 26 patients who underwent peritoneal implant excision (using both the CUSA and argon beam laser) were compared with seven patients without residual disease and without peritoneal implant excision and 34 patients who were cytoreduced to residual peritoneal implants of less than 1-cm in diameter. While the operative time in the peritoneal implant excision group was statistically significantly longer, survival was significantly greater (P=0.003) compared with that in the group with residual implants. No major morbidity was attributable to peritoneal implant excision. This study supports a meticulous attempt at total peritoneal implant excision in otherwise optimally cytoreduced ovarian cancer patients. A randomized, prospective study is needed to prove this.

In spite of well-trained, aggressive surgeons and modern technology, some patients with advanced ovarian cancer cannot be optimally cytoreduced. Examples of nonresectability include extensive liver parenchymal disease, involvement of the superior mesenteric vessels, and involvement of the porta hepatitis. Some patients will have overwhelming disease, and others will be too medically compromised to tolerate extensive surgery. In our experience, only 20% to 25% of patients fit in this category.

### Secondary Cytoreduction

Although the scientific basis is not perfect, aggressive cytoreductive surgery is widely accepted in the initial management of ovarian cancer patients. However, the role of secondary cytoreductive surgery is not so well defined. The term secondary cytoreductive surgery encompasses a variety of different clinical scenarios (Table 1).

The evidence for the value of secondary cytoreductive surgery in each situation is retrospective in nature except in its use as an interval procedure after suboptimally primary cytoreductive surgery. An initial report\[33\] in 1983 suggested some value for secondary cytoreductive surgery in general involved 32 patients, of whom 11 had no clinical evidence of disease and 21 had clinical evidence of disease. Twelve patients were optimally cytoreduced (largest diameter of residual disease was less than 1.5 cm) with a median survival of 20 months, and 20 patients could not be optimally cytoreduced with a median survival of five months. This difference in survival was statistically significant (P<0.01). Survival also was statistically superior in patients cytoreduced with no clinical evidence of disease compared with those cytoreduced with clinical evidence of disease.

Subsequent reports have been more focused. Several retrospective studies have analyzed patients undergoing second-look laparotomy with no clinical evidence of disease. Table 2 summarizes these studies with regard to median survival and the maximum size of residual disease.[34-37] In the study by Lippman et al\[34\] survival in the optimally cytoreduced group dramatically improved compared with that in the suboptimally cytoreduced group. The most dramatic survival advantage in studies by Hoskins and colleagues\[36\] and by Podratz et al\[37\] was seen in those patients whose gross residual disease was completely removed. In neither study was the median survival reached in this group of patients.

Patients with clinical evidence of disease at the completion of primary chemotherapy probably do not benefit significantly from secondary cytoreduction. This is particularly true for patients who progress during chemotherapy. Evidence to this effect is shown in a report\[38\] involving patients with clinical evidence of disease prior to second-look laparotomy. Of 77 patients, 32 were optimally cytoreduced and 45 had suboptimal residual disease. Both groups had a median survival of 12 months.

Secondary cytoreductive surgery may be of benefit in patients with recurrent ovarian cancer after a significant disease-free interval. Janicke et al\[39\] aggressively debulked 30 patients in this category and were able to completely remove disease in 14 patients. In 12 patients, gross residual disease was less than 2 cm, and bowel resection was necessary in 19 patients. Median survival for those with completely resected disease and those with gross residual disease of less than 2 cm was 29 months and nine months, respectively. The most significant factors associated with improved survival in this study included absence of gross residual disease and a disease-free interval of more than 12 months. Patients with a disease-free interval of six months or less seldom benefit from secondary cytoreductive surgery.

Interval cytoreduction after suboptimal initial surgery in apparent responders to chemotherapy has been examined more critically. Wiltshaw et al\[40\] demonstrated a significant survival advantage in partial responders who underwent secondary cytoreduction vs partial responders who did not undergo surgery. In addition, a prospective, randomized study\[41\] by the European Organization for Research and Treatment of Cancer (EORTC) demonstrated a statistically significant improvement in both disease-free and overall survival in the interval surgery group. In this study involving 278 evaluable patients, 140 were assigned to the interval surgery arm.
Residual disease larger than 1 cm was present in 83 patients in this arm, and the disease could be cytoreduced to less than 1 cm in greatest diameter in 37 of these patients. This surgery was primarily composed of removal of ovaries that remained after initial surgery. There was no operative mortality, and morbidity was minimal. Of interest, however, is the lack of difference in complete pathologic responders in the two arms. While interval surgery may improve survival, it does not necessarily lead to an ultimate cure. Nonetheless, the results of the EORTC study are compelling. A similar study is being conducted by the Gynecologic Oncology Group to confirm these results.

The benefit of secondary cytoreductive surgery in advanced ovarian cancer is dependent on patient selection. Ideal candidates are those with suboptimal initial surgery and response to chemotherapy, patients without clinical evidence of disease at the time of second-look laparotomy in whom all gross disease can be removed, and patients with recurrent disease after a prolonged disease-free interval. The aggressiveness with which secondary cytoreduction should be pursued is questionable. A total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed if not done initially. Aggressive specialized procedures such as bowel resection may be of value in this setting, although evidence to that effect is lacking.

Conclusions

Careful staging and optimal cytoreduction is the desirable standard of care for patients with ovarian cancer. Such surgery has been facilitated by newer instrumentation. There is good evidence that secondary cytoreduction is of benefit in selected patients, but it is unlikely that evidence from prospective randomized trials to document the value of primary cytoreduction will ever be produced.

References


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