Surgical Cytoreduction in Ovarian Cancer

By Wayne A. Mccreath, MD and Dennis S. Chi, MD

The majority of ovarian cancer patients present with advanced-stage disease, for which the goal of surgery is not only to document the extent of disease but also to perform surgical cytoreduction or tumor debulking. Cytoreductive surgery for ovarian cancer is generally performed at the time of diagnosis, when it is referred to as primary cytoreduction. It is also performed during primary chemotherapy (interval cytoreduction) and after disease recurrence (secondary cytoreduction). Over the past 3 decades, numerous retrospective analyses have established the role of primary cytoreduction in the management of advanced-stage ovarian cancer. However, recent studies have reported that certain patients benefit from a neoadjuvant chemotherapeutic approach, in which chemotherapy is given to those with presumed advanced ovarian cancer prior to cytoreductive surgery. Although several theoretical advantages of this approach over primary cytoreduction have been reported, significant concerns remain. The role of neoadjuvant chemotherapy is being investigated in a randomized study currently being conducted by the European Organization for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada. The benefit of interval cytoreduction was investigated in two randomized prospective trials conducted by the EORTC and the Gynecologic Oncology Group (GOG). Final results were somewhat conflicting, but both studies supported an extensive attempt at surgical cytoreduction during primary therapy. In the management of recurrent disease, the majority of retrospective studies demonstrate a benefit to secondary cytoreduction. The GOG is currently attempting to better define the role of secondary cytoreduction in a prospective, randomized trial.

Ovarian cancer is the third most common cancer of the female reproductive tract, yet has the highest case fatality ratio of all gynecologic malignancies. Every year, approximately 23,000 American women are diagnosed with the disease and about 14,000 die, despite aggressive management.[1,2] One of the main reasons for the high fatality ratio among ovarian cancer patients relates to the fact that the majority are diagnosed with advanced disease. Table 1 summarizes the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian cancer.[3] The distribution by FIGO stage of over 4,000 ovarian cancer patients is presented in Table 2.[3] Surgery followed by chemotherapy is the standard approach to the management of ovarian cancer. Despite many chemotherapeutic advances over the past 2 decades, surgery remains the cornerstone of effective disease management. For patients who present with early-stage disease, surgery involves a comprehensive staging procedure with the goal of thoroughly evaluating the peritoneal cavity and the retroperitoneum to identify clinically inapparent sites of metastasis. The rationale and procedures performed during staging are described elsewhere and are not the focus of this review.[4] For patients with advanced-stage ovarian cancer, the goal of surgery is cytoreduction or tumor debulking. "Primary" cytoreduction is performed at the time of diagnosis, prior to the initiation of cytotoxic chemotherapy. In cases of suboptimal primary cytoreduction, "interval" cytoreduction has been described as a second attempt at surgical debulking after the initiation of primary chemotherapy, but prior to its completion. "Secondary" cytoreduction generally refers to surgical debulking performed at the time of disease recurrence. The role of surgical cytoreduction in the management of advanced and recurrent ovarian cancer is the subject of this review.
Primary Cytoreduction

As stated previously, the majority of ovarian cancer patients present with advanced disease, for which the goal of surgery is to document the stage and extent of the disease, and more importantly, to resect as much grossly visible tumor as possible with the knowledge that microscopic and perhaps macroscopic tumor will be left behind. For most solid tumors, such as lung, pancreatic, and gastric cancer, surgical "cytoreduction" or "debulking" has no role in management because no effective chemotherapy protocol exists for these malignancies. However, there are effective chemotherapy protocols for ovarian cancer. Consequently, both theoretical and clinical benefits have been demonstrated after surgical cytoreduction for the majority of newly diagnosed cases of ovarian cancer, as well as in select cases of recurrent disease. Theoretical Benefits

The most important theoretical effect of primary cytoreductive surgery is its impact on the chemosensitivity of the residual tumor nodules. Chemotherapeutic agents exert maximum cytotoxicity on tumors that are adequately perfused, well differentiated, and have a high mitotic index. Smaller-volume residual tumors after cytoreduction have an adequate blood supply creating...
an oxygen- and nutrient-rich environment that promotes cell division. Bulky noncytoreduced tumors, however, outgrow their blood supply, creating a nutrient-deficient and hypoxic environment that halts cell division. Cytoreduction, therefore, maximizes the chemotherapeutic response because the cell-cycle-specific and -nonspecific chemotherapeutic agents act when the cells have a high mitotic rate and are, therefore, most susceptible to cytotoxic drugs.

**Clinical Benefits**

Griffiths[5] was the first investigator to quantify the diameter of the largest residual tumor in relation to chemotherapy response rates and survival. He demonstrated an inverse relationship between maximal residual tumor and patient survival. Since his landmark study, many authors have confirmed their observations.[6-9] Today, the majority of studies use the diameter of the largest remaining tumor nodule as the measurement of residual disease. Patients are divided into optimal and suboptimal groups, using a variety of cutoff points—from any visible disease to 3 cm—to define optimal cytoreduction. Overall, a clear clinical benefit is observed when patients are optimally cytoreduced. These patients have higher response rates to chemotherapy and also have higher median survivals.[10] In two large Gynecologic Oncology Group (GOG) studies, Hoskins et al further clarified the role of primary cytoreductive surgery in patients with advanced ovarian cancer.[6] In the first study, the survival of patients who were found to have abdominal disease ≥ 1 cm during surgery was compared to that of patients with abdominal disease of ≥ 1 cm that had then been surgically cytoreduced to ≤ 1 cm. If surgery was the only important prognostic factor, then survival should have been the same in the two groups. However, patients with small-volume disease survived longer than patients who were cytoreduced to small-volume disease. Further analysis showed that the age of the patient, the grade of the tumor, and the number of residual tumor nodules were independent prognostic factors. Although this study did not show primary cytoreduction to be ineffective, it did show that other factors, including tumor biology, were also important. In the second study, cytoreduction to ≤ 2-cm residual disease resulted in a significant survival benefit, but all residual diameters > 2 cm had equivalent survival. Therefore, unless cytoreduction resulted in the maximum residual tumor diameter being ≤ 2 cm, surgical cytoreduction did not improve survival.[11] Three distinct groups of patients emerged from these two studies: (1) those with no grossly visible residual disease; (2) those with optimal residual disease (≤ 2 cm); and (3) those with suboptimal disease (> 2 cm in diameter). The 4-year survival rates for these patients were 60%, 35%, and 20%, respectively. Table 3 summarizes the largest studies in the literature from both cooperative groups[12,13] and single institutions[ 14-16] that have analyzed the survival of patients with stage III ovarian cancer by optimal cytoreduction. Overall, a clear clinical benefit is observed when patients are optimally cytoreduced.

### Optimal Cytoreduction Parameters

- Although the benefits of optimal cytoreduction for advanced ovarian cancer appear to be well established, as Table 3 demonstrates, the most appropriate cutoff point for optimal cytoreduction remains controversial. In his seminal paper, Griffith[ 5] used 1.5 cm as the cutoff point in defining optimal cytoreduction. Other authors have used values between any visible disease and 3 cm. In 2001, we reported a 28% survival for patients with > 2 cm residual disease who were cytoreduced to between 1- and 2-cm residual disease, which was not significantly different from the 21% 5-year survival of patients with > 2-cm residual disease. These survival rates were both significantly lower than the 50% 5-year survival for patients cytoreduced to ≤ 1 cm. These data support the current GOG definition of optimal cytoreduction as that with residual disease ≤ 1 cm.[16] At our institution, the rates of optimal cytoreduction for advanced ovarian cancer historically have been less than 50%. In January 2001, with strong data supporting the survival benefits of optimal cytoreduction,[ 12-16] our service began incorporating the use of extensive upper abdominal cytoreductive procedures including diaphragm-stripping/resection, splenectomy, distal pancreatectomy, liver resection, resection of tumor from the porta hepatitis, and cholecystectomy, if needed, to achieve optimal (≤ 1-cm residual) cytoreduction. We studied two separate groups of patients. Group 1 consisted of patients who had their primary surgery at our institution between November 1998 and May 2000—a time when extensive upper-abdominal procedures were not utilized during primary cytoreductive procedures. Group 2 patients underwent their primary surgery between January 2001 and May 2002—a time when a more aggressive approach to surgical cytoreduction was used. In the first group of patients, optimal cytoreduction was attained in 50% of patients, compared to 76% in the second group (P < .01). Although operative time and estimated blood loss increased, complications did not increase significantly.[19]
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remove virtually all visible disease. The main, new technologic advances consist of the cavitational ultrasonic surgical aspirator and the argon-beam coagulator. Bristow and Montz[20] have shown the feasibility and success of surgical cytoreduction using the argon-beam coagulator. They reported that the use of this device resulted in a 94% successful cytoreduction rate, compared to 64% without it. In a similar study, patients cytoreduced with the cavitational ultrasonic surgical aspirator had lower morbidity, decreased length of hospital stay, and a lower serum level of CA-125 at 1 and 2 months postsurgery, compared to patients not cytoreduced with this technology.[21]

Table 2
Distribution by FIGO Stage of Ovarian Cancer Patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1,449 (33%)</td>
</tr>
<tr>
<td>II</td>
<td>386 (9%)</td>
</tr>
<tr>
<td>III</td>
<td>2,034 (46%)</td>
</tr>
<tr>
<td>IV</td>
<td>507 (12%)</td>
</tr>
<tr>
<td>Total</td>
<td>4,376 (100%)</td>
</tr>
</tbody>
</table>

FIGO = International Federation of Gynecology and Obstetrics.
Adapted from Heintz et al.[3]

Meta-analyses
Despite numerous studies demonstrating improved survival of advanced ovarian cancer patients who were optimally cytoreduced, critics argue that it is not the surgical cytoreduction that leads to prolonged survival, but rather, the inherent biology of the tumor (which also enables optimal cytoreduction). The meta-analysis by Hunter and colleagues[22] is often cited to support this argument. They analyzed 58 articles encompassing 6,962 advanced ovarian cancer patients and found that a 10% increase in maximal cytoreductive surgery resulted in a 4.1% increase in median survival. However, the use of platinum-based chemotherapy produced an estimated 53% increase in median survival. Hunter et al concluded that surgery had a minor effect on the survival of women with advanced ovarian cancer. This meta-analysis has been criticized because of the low rate of optimal debulking and the lack of treatment with optimal platinum-containing chemotherapy.[23] More recently, Bristow et al[24] performed a meta-analysis on the survival effect of maximal cytoreduction for ovarian cancer during the era of platinum-based chemotherapy. This analysis evaluated 81 studies involving 6,885 patients with stage III/IV ovarian cancer and found that during the platinum era, maximum cytoreduction was a powerful determinant of cohort survival. These investigators showed further that each 10% increase in maximal cytoreduction resulted in a 5.5% increase in median survival. They concluded that expert centers with optimal cytoreduction rates of 75% or greater offered a 50% increase in median survival over less experienced centers with optimal cytoreduction rates of 25% or less.
Stage IV Disease

The role of primary cytoreduction in the management of stage III disease is well defined; however, its benefit in stage IV disease is not as clear. Most studies that address survival in ovarian cancer patients evaluate only stage III disease or a combination of stage III and IV disease. In stage IV disease—which by definition includes extraperitoneal or intrahepatic metastasis—the benefit of surgical cytoreduction has been questioned. An early study by Wharton et al[25] reported a 4-year survival of 9% in patients who were cytoreduced to ≤ 2 cm. This study was performed before the platinum-based chemotherapy era, which may explain the poor outcomes.[25] Additionally, Goodman et al reported no significant survival advantage for patients who underwent optimal cytoreductive surgery for stage IV epithelial ovarian cancer compared to patients who were suboptimally cytoreduced.[26] Contrary to these reports, most other studies have shown a survival advantage for primary cytoreduction in patients with stage IV ovarian cancer.[17,27] Curtin and colleagues[17] reported on 97 patients with stage IV disease, of which 51% were optimally cytoreduced (residual disease ≤ 2 cm). Median survival for the optimally vs suboptimally cytoreduced group was 40 vs 18 months (P = .0136). Bristow and investigators[27] have also shown the value of optimal debulking in stage IV patients with liver metastases. In this study, patients with optimal hepatic and extrahepatic residual disease had a median survival of 50.1 months, compared to 27 months for those with suboptimal hepatic but optimal extrahepatic residual disease, and 7.6 months for patients with both suboptimal hepatic and extrahepatic residual disease. Table 4 summarizes recent studies of surgical cytoreduction for stage IV ovarian cancer.[17,26-30]

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy, which is given to patients with advanced ovarian cancer prior to cytoreductive surgery, has several theoretical advantages over primary cytoreduction. These include (1) improvement of performance status, especially in elderly patients and those with pleural effusions and ascites, (2) decrease in the extent and morbidity of surgery by reducing tumor volume preoperatively, and (3) increase in the percentage of patients undergoing optimal cytoreduction. Several retrospective studies have evaluated this approach, but
to date, no prospective randomized data exist. Vergote et al[31] reported on 285 patients with advanced ovarian cancer treated between 1980 and 1997. In the period from 1980 to 1988, all patients underwent primary debulking surgery. From 1989 to 1997, patients were surgically evaluated to determine whether they should receive primary chemotherapy (43%) or primary cytoreductive surgery (57%). The crude 3-year survival in the later part of the study was 42%, compared to 26% during the earlier period, when all patients underwent primary debulking surgery. Ansquer et al[32] reported the French multicenter experience with neoadjuvant chemotherapy for ovarian cancer deemed unresectable by either laparoscopy (61%) or laparotomy (39%). Patients received a median of four cycles of chemotherapy preoperatively, with 80% responding to chemotherapy and subsequently undergoing debulking, which was optimal in 91%. The authors concluded that neoadjuvant chemotherapy in unresectable ovarian cancer led to the selection of chemo-sensitive patients who, in the majority of cases, could subsequently undergo optimal cytoreduction. In addition, aggressive cytoreduction was avoided in patients with initial chemoresistance. Table 5 summarizes the studies that have compared the neoadjuvant approach to standard primary cytoreduction.[ 33-36] Many of the patients managed with neoadjuvant chemotherapy had significant medical comorbidities, and except for the series reported by Kuhn and colleagues,[ 35] none of the median survivals using the neoadjuvant chemotherapy approach those attained with optimal primary cytoreduction. Therefore, many authorities are hesitant to uniformly use this strategy, because it may result in a significant number of patients being deprived of the opportunity for optimal cytoreduction and 5-year survival rates of up to 50%. However, if preoperative evaluation could predict which patients had disease so extensive that optimal cytoreduction could not be performed, these patients would be ideal candidates for neoadjuvant chemotherapy. Retrospective studies have evaluated the accuracy of computed tomography (CT) scanning and serum CA-125 level in selecting candidates for optimal cytoreduction. These studies report sensitivities, specificities, positive predictive values, and negative predictive values ranging from 50% to 100%, 63% to 100%, 61% to 100%, and 75% to 100%, respectively.[ 37-40] We are currently evaluating the ability of preoperative CT scan and serum CA-125 to predict optimal primary cytoreduction for patients with advanced ovarian cancer in a multicenter prospective trial.

<table>
<thead>
<tr>
<th>Author</th>
<th>Residual Disease</th>
<th>Number of Patients</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodman et al, 1992[26]</td>
<td>&lt; 2 cm</td>
<td>23</td>
<td>28 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>12</td>
<td>22 mo</td>
</tr>
<tr>
<td>Curtin et al, 1997[17]</td>
<td>&lt; 2 cm</td>
<td>41</td>
<td>40 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>51</td>
<td>18 mo</td>
</tr>
<tr>
<td>Liu et al, 1997[28]</td>
<td>&lt; 2 cm</td>
<td>14</td>
<td>37 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>33</td>
<td>17 mo</td>
</tr>
<tr>
<td>Munkarah et al, 1997[29]</td>
<td>&lt; 2 cm</td>
<td>31</td>
<td>25 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>61</td>
<td>15 mo</td>
</tr>
<tr>
<td>Bristow et al, 1999[27]</td>
<td>&lt; 1 cm</td>
<td>25</td>
<td>38 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 cm</td>
<td>59</td>
<td>10 mo</td>
</tr>
<tr>
<td>Akahira et al, 2001[30]</td>
<td>&lt; 2 cm</td>
<td>155</td>
<td>32 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>70</td>
<td>16 mo</td>
</tr>
</tbody>
</table>
The role and indications for neoadjuvant chemotherapy may be further elucidated after the completion of a randomized prospective trial being performed jointly by the European Organization for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCI-C). In this trial, patients with biopsy-proven stage IIIC/IV ovarian cancer will be randomized to primary cytoreduction vs neoadjuvant chemotherapy. Both arms will receive six cycles of paclitaxel and platinum chemotherapy. The trial is expected to close to accrual in 2005.[23]

**Interval Cytoreduction**

The actual percentage of advanced ovarian cancer patients who can be successfully cytoreduced to optimal residual disease status at the time of the initial surgical procedure ranges in the literature from 17% to 85%, with a mean of approximately 35%. [4,10,13,24] A substantial number of these patients, therefore, will be suboptimally cytoreduced.

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**Table 5**

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 1999[33]</td>
<td>Surgery</td>
<td>206</td>
<td>26 mo</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant</td>
<td>59</td>
<td>13 mo</td>
</tr>
<tr>
<td>Surwit et al, 1999[34]</td>
<td>Surgery</td>
<td>103</td>
<td>28 mo</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant</td>
<td>61</td>
<td>27 mo</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant</td>
<td>32</td>
<td>42 mo</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant</td>
<td>20</td>
<td>26 mo</td>
</tr>
</tbody>
</table>

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**Table 6**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segna et al, 1993[55]</td>
<td>100</td>
<td>Residual disease (optimal &lt; 2 cm), disease-free interval, age, residual after primary surgery, response to primary platinum treatment</td>
</tr>
<tr>
<td>Zang et al, 2000[56]</td>
<td>106</td>
<td>Residual disease (optimal &lt; 1 cm), disease-free interval, ascites</td>
</tr>
<tr>
<td>Eisenkop et al, 2000[57]</td>
<td>106</td>
<td>Residual disease (optimal no gross), disease-free interval, chemotherapy before surgery, size of largest recurrent tumor</td>
</tr>
<tr>
<td>Scarabelli et al, 2001[58]</td>
<td>149</td>
<td>Residual disease (optimal ≤ 1 cm), disease-free interval, prior chemotherapy regimen</td>
</tr>
<tr>
<td>Chi et al, 2003[59]</td>
<td>149</td>
<td>Residual disease and disease-free interval</td>
</tr>
</tbody>
</table>

*N ≥ 100.

Because patients with suboptimal residual disease carry such a poor prognosis, their further management is especially challenging. Some investigators have evaluated the benefit of a brief course of chemotherapy, followed by a second attempt at cytoreduction before completing a prescribed
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A survival benefit has been demonstrated for patients with recurrent ovarian cancer who undergo secondary cytoreduction. However, in all other published series, a follow-up study in 25 patients conducted by Munkarah et al[29] from the same institution also found no statistically significant benefit for secondary cytoreduction. A point of 2 cm for optimal debulking, found no survival benefit for secondary cytoreduction. A study by Morris et al[52] subsequently studied 30 patients with recurrent ovarian cancer and, using a cutoff point of 2 cm for optimal debulking, found no survival benefit for secondary cytoreduction. A follow-up study in 25 patients conducted by Munkarah et al[29] from the same institution also found no statistically significant benefit for secondary cytoreduction. However, in all other published series, a survival benefit has been demonstrated for patients with recurrent ovarian cancer who undergo:

Secondary Cytoreduction

Up to 85% of patients with advanced ovarian cancer who undergo primary surgical cytoreduction and adjuvant chemotherapy will develop recurrent disease.[46] When recurrence occurs, additional chemotherapy is usually administered with the goal of attaining a second clinical remission. Generally, what determines the choice of chemotherapy in this setting is the platinum-free interval. A patient is considered platinum-resistant if disease progression occurs during chemotherapy, or if recurrence occurs within 6 months of the completion of treatment. Patients who are platinsensitive and disease-free for at least 6 months after completing chemotherapy[ 47] are usually re-treated with platinum-based chemotherapy in light of the initial response. Platinum-resistant patients, however, are generally treated with other chemotherapeutic agents, such as liposomal doxorubicin (Doxil), topotecan (Hycamtin), and gemcitabine (Gemzar). The overall prognosis for these patients is poor, and they are often recruited for experimental clinical trials. Response rates in patients treated with second-line chemotherapy range from 14% to 34%. [48-51] Secondary cytoreduction has not been shown to improve survival or quality of life for patients with platinum-refractory disease.[52,53] In selected platinum-sensitive patients, however, this strategy is thought to provide a survival benefit. The first study to describe the value of secondary cytoreduction for recurrent ovarian cancer was conducted by Berek and colleagues,[54] who demonstrated that patients who undergo optimal debulking (defined as residual disease ≤ 1.5 cm) at the time of secondary cytoreduction have a median survival of 20 months, compared to 5 months for those who are suboptimally debulked. In this study, Berek et al reported duration from therapy, symptoms, ascites, and initial tumor mass as important prognostic factors for survival. Morris et al[52] subsequently studied 30 patients with recurrent ovarian cancer and, using a cutoff point of 2 cm for optimal debulking, found no survival benefit for secondary cytoreduction. A follow-up study in 25 patients conducted by Munkarah et al[29] from the same institution also found no statistically significant benefit for secondary cytoreduction. However, in all other published series, a survival benefit has been demonstrated for patients with recurrent ovarian cancer who undergo:

Study Differences

The main differences between the EORTC and GOG trials were the chemotherapeutic agents used, type of surgeon involved, and extent of the primary surgery. In the EORTC trial, the primary surgery did not need to be performed by a gynecologic oncologist, whereas in the GOG trial, a gynecologic oncologist frequently performed the primary surgery, and presumably, an aggressive attempt was made to attain optimal cytoreduction. Moreover, the EORTC study enrolled patients with stage IV disease and a higher proportion of patients with poor performance status, and thereby included a substantial number of patients who underwent less aggressive attempts at primary cytoreduction. Taking all these factors into account, it appears interval debulking surgery does not offer a survival benefit to patients who initially undergo a maximal surgical effort by a gynecologic oncologist.[23]
optimal secondary cytoreduction. Table 6 summarizes the largest reported series on secondary cytoreduction for recurrent ovarian cancer. [55-59] In all the series listed, residual disease and disease-free interval prior to the secondary cytoreduction were found to be independent prognostic factors. [55-59] Although the majority of studies demonstrate a benefit to secondary cytoreduction, they all analyze heterogeneous groups of patients and surgeons, involve tumors with different biologic behavior, are retrospective in nature, and have strong selection biases in their criteria for surgical interventions. [60] A randomized prospective trial to fully evaluate secondary cytoreductive surgery is currently being performed. This study, GOG 202, is a bifactorial, randomized controlled trial of sequence-dependent chemotherapy and secondary cytoreductive surgery in platinum-sensitive recurrent ovarian and primary peritoneal cancers. Patients with recurrent disease will be randomized to either treatment with topotecan or carboplatin (Paraplatin) or secondary cytoreduction followed by treatment with either agent. **Summary** Surgical cytoreduction in ovarian cancer refers to the removal of as much macroscopic disease as possible, with the knowledge that microscopic and perhaps macroscopic tumor will be left behind. This surgical approach maximizes the chemotherapeutic response by allowing chemotherapeutic agents to act when the cells are most mitotically active. Numerous studies analyzing prognostic factors for advanced ovarian cancer have demonstrated the benefits of optimal cytoreduction on survival. Cytoreduction does not prolong survival, if it is suboptimal. The cutoff for the definition of optimal vs suboptimal varies from institution to institution and has changed numerous times over the past 3 decades. However, most gynecologic oncologists and the GOG currently define optimal cytoreduction as that which leaves residual disease ≤ 1 cm. Due to the propensity of the intraperitoneal distribution of advanced ovarian cancer, it is often necessary to use extensive upper-abdominal and pelvic procedures to achieve optimal cytoreduction. These procedures should be performed in expert centers, as those institutions with optimal cytoreduction rates greater than 75% offer a 50% increase in median survival compared to less-experienced centers. Although studies of neoadjuvant chemotherapy have demonstrated reduced surgical morbidity and increased rates of optimal cytoreduction after a few cycles of chemotherapy, in virtually all series, the median survivals are no better than those achieved with primary suboptimal debulking. The concern about the neoadjuvant approach is that patients who could potentially be optimally cytoreduced may be deprived of the approach that offers them the highest 5-year survival rates and the longest median survival. Therefore, we reserve the neoadjuvant approach for patients with poor performance status and/or disease that is obviously not amenable to optimal cytoreduction. Prospective studies to preoperatively predict optimal primary cytoreduction are ongoing. The true benefit of neoadjuvant chemotherapy hopefully will be clarified after the completion of the EORTC-Gynaecological Cancer Group and NCI-C trials. Similarly, the role of interval cytoreduction is not clear, as there are conflicting results from two large randomized trials. In cases in which a valid attempt at primary cytoreduction was made by a gynecologic oncologist, interval cytoreduction most likely produces no benefit. However, if a valid attempt was not made, an interval cytoreduction may improve survival. Patients with platinum-sensitive recurrent ovarian cancer appear to benefit from secondary cytoreduction. However, patients undergoing surgery in this setting have been highly selected in the reported series to date. Thus, many questions remain regarding the specific situations in which secondary cytoreduction should be implemented. A randomized trial currently being performed by the GOG will help clarify the role of secondary cytoreduction in the management of recurrent ovarian cancer. With many questions still left unanswered, surgical management of ovarian cancer remains a challenge.

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