Cytoreductive Surgery for Advanced Ovarian Cancer: Quo Vadis?

Review Article [1] | September 15, 2011
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This article focuses on the recent debate regarding when—or whether—patients with ovarian cancer should undergo aggressive surgical resection.

The Latin phrase *quo vadis*, meaning "whither goest thou?" or "where are you going?," aptly reflects the current uncertainty in the gynecologic oncology community about how best to care for women with advanced ovarian cancer. The controversy is especially relevant since ovarian cancer mortality exceeds the combined mortality of all other gynecologic malignancies in the United States. Currently, it is the ninth leading cause of cancer in women but the fifth leading cause of all cancer-related deaths. In 2010, there were an estimated 21,880 new cases and 13,850 deaths.[1] One in 78 women (1.3%) in the US will be diagnosed with this highly lethal disease during their lifetime. Worldwide each year, approximately 225,000 women are diagnosed with ovarian cancer and more than 140,000 die.[2]

**TABLE 1**

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<th>Symptoms of Ovarian Cancer</th>
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<td>Ovarian cancer is often portrayed as the disease that &quot;whispers&quot; because it does not present with dramatic bleeding, excruciating pain, or an obvious lump. Instead, the typical symptoms (Table 1) tend to be indolent. Patients and their healthcare providers often attribute such nonspecific changes to menopause, aging, dietary indiscretions, stress, depression, or functional bowel problems. Frequently, women are medically managed for indigestion or other presumed ailments without having a pelvic examination.[3] As a result, substantial delays prior to diagnosis are very common.</td>
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**FIGURE 1**

Omental Caking

Unfortunately, there is no effective screening test. Routine checks of serum CA125 markers or transvaginal sonograms do not result in early detection or reduced mortality in either the general or high-risk populations.[4] Two-thirds of women still present, as they always have, with advanced disease typically characterized by ascites, carcinomatosis, and omental caking (Figure 1). In the United States, less than half of such patients will be cared for by a gynecologic oncologist.[5] Instead, the majority are managed by physicians not necessarily familiar with the expected, often...
dramatic, response of ovarian cancer to aggressive treatment even in the setting of widespread disease. For example, a consulting general surgeon may perform a diverting colostomy for obstructive symptoms and afterwards the patient might be treated with a limited duration of single-agent palliative chemotherapy—or worse, directed to hospice. When a gynecologic oncologist is involved, survival is demonstrably improved. Patients are more likely to undergo both a comprehensive de-bulking procedure and postoperative combination chemotherapy.[6] Removal of bulky tumors as part of cancer treatment is an easy concept for patients and their families to understand. When ovarian cancer is initially suspected, they are usually anticipating an operation and are often greatly relieved when their gynecologic oncologist declares that "more than 90% of the tumor was removed" at the time of surgery. While sounding impressive, the actual benefits usually do not match up with patient expectations. In theory, fewer cancer cells at the start of chemotherapy should lead to a higher likelihood of cure. However, by the time advanced ovarian cancers are diagnosed, approximately 10¹⁰ to 10¹¹ malignant cells are present. Optimal debulking that removes an estimated 90% of the aggregate tumor represents 1 log cell kill. In contrast, one course of chemotherapy may produce up to a 2 to 3 log cell kill, representing a 99.0% to 99.9% reduction in tumor cells. Still, despite the often pronounced chemosensitivity, some tumor cells almost invariably persist.

Recent evidence suggests that metastatic ovarian cancers, like other solid tumors, contain a small subpopulation of highly specialized stem cells that escape cytoreductive procedures and have the capacity to evade current chemotherapeutic strategies. This "cancer stem cell hypothesis" postulates that tumors contain phenotypically distinct populations of stem-like cells with self-renewal capacity and the potential to reconstitute the entire cellular heterogeneity of a tumor. Ovarian cancer stem cells are thought to be responsible for tumor initiation, maintenance, and growth.[7] Ineffective targeting of this cell population is responsible for the therapeutic failures and tumor recurrences currently observed.[8]

Theoretical Arguments for Debulking Surgery

Owing to the comparable level of chemosensitivity and the likely existence of ovarian cancer stem cells, the actual clinical benefits of debulking have been harder to prove. Several supportive, but mostly theoretical, additional arguments have been proposed to justify the biological plausibility of debulking (Table 2).[9] Within the broader field of oncology, the aggressive surgical approach to widely metastatic disease is rather specific to ovarian cancer. Patients definitely do appear to benefit from one maximal debulking attempt, but the timing of the procedure and what defines a success have become increasingly controversial.

**Primary Debulking Surgery**

![Figure 2](image-url)
**En Bloc Splenectomy With Distal Omentectomy**

Joe V. Meigs, a gynecologic surgeon at Massachusetts General Hospital, initially described ovarian tumor debulking in 1934.[10] The concept did not gain traction until the mid 1970s, when C. Thomas Griffiths published his seminal paper on the subject.[11] Case series and other retrospective data accrued rapidly thereafter to further establish primary cytoreductive surgery as the de facto standard of care.[12,13]

The success of the operation depends on numerous factors, including patient selection, tumor location, and surgeon expertise. To achieve a survival benefit, an optimal result was initially defined as no residual tumors that individually measure more than 2 cm in size.[14] For purposes of uniformity, the Gynecologic Oncology Group (GOG) re-defined "optimal" debulking as residual implants ≤ 1 cm. For the past few decades, this criterion has served as the benchmark of success. Patients undergoing optimal primary cytoreductive surgery (≤ 1 cm residual disease), followed by intraperitoneal platinum-based chemotherapy, have a median overall survival of 66 months —the longest survival duration ever reported in a phase III study of ovarian cancer.[15] The level of success achieved in this GOG trial (protocol #172) is currently the gold standard for comparisons of any other treatment sequence.

**Survival Effect of Maximal Cytoreductive**

Despite the accumulated evidence supporting the importance of primary debulking, it remains controversial whether the better outcome is due to the surgeon's technical proficiency or some ill-defined, intrinsic feature of the cancer that makes the tumor implants easier to remove.[16,17] In general, extensive upper abdominal disease is strongly indicative of an aggressive tumor biology.[18] Although this is a common location of unresectable disease, optimal debulking may still be achieved in many of these patients by performing "ultra-radical" procedures, such as splenectomy (Figure 2) or diaphragmatic resection.[19,20] However, it is still unclear what impact ultra-radical techniques have on quality of life and morbidity. In addition, the cost-effectiveness of this intervention has not been investigated.[21] Regardless, survival rates have been shown to improve when the surgical paradigm is revised to a more aggressive philosophy incorporating these and other radical techniques (Figure 3).[22,23] Patients referred to specialized centers where such radical procedures are commonly performed may anticipate higher rates of optimal debulking and improved survival without additional major morbidity.[24]

**Median Overall Survival of Advanced Ovarian Cancer Patients Undergoing Primary Cytoreductive Surgery**

**Success Rates of Primary Cytoreductive Surgery in Stage III and IV Ovarian Cancer**

One valid criticism of cytoreductive surgery is that the assessment of gross residual disease by the surgeon at the completion of the operation he or she performed is biased and subjective. Due to tissue induration, inadequate exploration, or other factors, inaccuracies in the assessment of residual tumor size are commonplace.[25] Perhaps because of the inability to reliably quantify the remaining...
disease, a recent subanalysis of accumulated data from several prospective GOG trials demonstrated that patients with 0.1 to 1.0 cm residual disease had marginally improved overall survival compared with patients who had > 1 cm residual disease if they had stage III ovarian cancer and no improvement if they had stage IV disease. In fact, a dramatic survival benefit was only achieved with complete resection to microscopic residual disease (Table 3).[26,27] Based on these findings and other similar reports, there is a growing consensus that optimal cytoreduction should be defined using a more stringent criterion. Raising the bar for debulking success accordingly decreases the proportion of patients with stage III-IV ovarian cancer in whom complete resection can be accomplished (Table 4). Although complete resection is often not feasible, cytoreduction to as little residual tumor as possible should always be the focus of aggressive surgical efforts, since each incremental decrease in residual disease below 1 cm may be associated with an incremental improvement in overall survival.[28]

Even when successful, the obvious disadvantage of radical cytoreductive surgery is that it may result in a prolonged postoperative recovery that is fraught with complications. The initiation of chemotherapy may be delayed—or worse, postponed indefinitely.[29,30] When an optimal result is not possible, the surgical approach should be limited in scope to avoid unnecessary postoperative morbidity.

Suboptimal Surgical Attempt: Interval Debulking Surgery

Unfortunately, preoperative CA125 levels, computed tomography (CT) scans, and physical examinations are often not reliable predictors of which patients can be optimally debulked. As a result, many patients with advanced ovarian cancer who are taken for surgery cannot be completely resected. Invariably, the final determination cannot be made until abdominal exploration.

Two phase III trials were conducted to determine whether a second interval debulking procedure was worthwhile after an unsuccessful initial attempt followed by a few courses of chemotherapy. A European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrated a 6-month median survival advantage in patients who were re-explored after three cycles of chemotherapy.[31] In contrast, no survival advantage was demonstrated when a similar study was conducted through the GOG.[32] These conflicting results are most easily explained by clarifying who performed the first surgery.

In the GOG trial, virtually all patients had their initial attempt at de-bulking performed by a gynecologic oncologist, whereas in the European study, relatively few had their first surgery performed by a subspecialist. Thus, interval debulking appears to yield benefit only in patients whose primary surgery was not performed by a gynecologic oncologist, those in whom the first try was not intended as a maximal resection of all gross disease, and those in whom no upfront surgery was performed at all.[33]

Neoadjuvant Chemotherapy With Interval Debulking Surgery

Some patients are too medically ill to initially undergo any type of abdominal operation, whereas others have disease that is obviously too extensive to be resected even by an experienced ovarian cancer surgical team. In these circumstances, neoadjuvant chemotherapy (NACT) is routinely used, ideally after the diagnosis has been confirmed by paracentesis or computed tomography-guided biopsy.[30] Following three to four courses of treatment, the feasibility of surgery can be reassessed. In some series, NACT followed by interval debulking has demonstrated comparable survival outcomes to those reported for primary surgery. Fewer radical procedures may be required, the rate of achieving minimal residual disease may be higher, and patients may experience less morbidity.[34,35] However, other reports have suggested that NACT in lieu of primary debulking is associated with an inferior overall survival.[36] Direct comparisons have historically been difficult to perform.

In 1986, the GOG and a collaborative group in the Netherlands each separately opened randomized phase III trials to test the hypothesis that primary debulking was superior to NACT in advanced ovarian cancer. Both studies were closed due to poor accrual. One prevailing opinion at the time regarding the reason for the poor accrual was that clinicians did not want to subject their patients to "substandard" NACT treatment. Until recently, the presumed benefits of primary surgical cytoreduction in advanced ovarian cancer had not been rigorously tested. The results of a randomized phase III trial conducted by the EORTC were first presented in October 2008 and subsequently published in September 2010.[30] These data have reignited the debate over how best to initially treat women with advanced ovarian cancer. In the study, 670 patients were
randomly assigned to either primary debulking surgery or NACT. After three courses of platinum-based treatment, patients in the NACT arm who demonstrated a response underwent interval debulking. The authors reported a median overall survival of 29 to 30 months, regardless of assigned treatment group. In the multivariate analysis, complete resection of all macroscopic disease at debulking surgery was identified as the strongest independent prognostic factor, but the timing of surgery did not seem to matter. However, postoperative infections, venous complications, fistula, hemorrhage, and postoperative mortality tended to be higher after primary debulking surgery. Based on the authors' interpretation of their data, NACT and interval debulking was the preferred treatment.

Despite these findings, most gynecologic oncologists in the United States report that they use NACT for less than 10% of advanced ovarian cancers.[37] Some European gynecologic oncologists have openly questioned what kind of evidence would be needed to convince their US colleagues of the superiority of the NACT approach.[38] At least two criticisms of the EORTC trial have been suggested as reasons that the results may not be applicable in the US. First, the duration of patient survival in the study was shorter than expected. Additionally, only 42% of the primary debulking operations resulted in an optimal result (≤ 1 cm of residual disease). Thus, it is possible that a more aggressive initial attempt might have led to a better outcome for the group randomized to surgery. A prospective phase III trial conducted within the US will need to be performed to sway opinion and markedly change the practice of gynecologic oncologists in this country. Meanwhile, the controversy will persist and individual patterns of care will continue.

**Secondary Debulking Surgery**

Although the rationale for a second debulking operation at the time of relapse is largely an extrapolation of the rationale for primary surgery, there are several reasons that the certainty of clinical benefit is even more contentious. Recurrent ovarian cancer has a much more heterogeneous presentation. As a result, treatment is typically more individualized. Secondary debulking is generally considered to be most effective when there is a single isolated relapse, when there has been a long disease-free interval after completion of primary therapy (ie, more than 12 months), when the patient is reasonably healthy, and when resection to minimal or no residual disease can be achieved. Women with symptomatic ascites, carcinomatosis, or early relapse (ie, < 6 months after primary treatment), or who are in poor condition, are least likely to benefit.[39,40] Most patients will fall somewhere between these clinical extremes. Chi et al[41] have proposed guidelines that are generally accepted, but in practice each gynecologic oncologist uses his or her own criteria for determining which, if any, patients are good candidates for secondary surgery. The previously reported retrospective series largely reflect this selection bias. Consequently, the success rates of optimal secondary debulking surgery and the corresponding survival data vary broadly. The potential for significant morbidity and the notable lack of benefit for patients who are left with residual disease underscore the importance of careful counseling and preoperative assessment of patients. Predictably, complete resection appears to be associated with the most prolonged postoperative survival.[42]

Three large, prospective randomized phase III studies are currently underway within the EORTC (protocol #55963), the GOG (protocol #213), and Arbeitsgemeinschaft Gynaekologische Onkologie (DESKTOP OVAR trial). They were each designed to evaluate the value of secondary debulking in the treatment of relapsed ovarian cancer. Unfortunately, it will be years before the final results are available. In the meantime, practice patterns will largely continue to be guided by the results of retrospective studies.

**Conclusion**

Primary debulking surgery that achieves complete resection to no macroscopic residual disease has consistently demonstrated the best long-term outcome of any treatment strategy in advanced ovarian cancer. Since radical procedures are routinely required, surgically experienced centers that embrace an aggressive surgical paradigm have the highest reported rates of success. However, even at these sites, the likelihood of complete resection ranges from 15% to 30% of patients taken to surgery.[24,28] When complete resection is not feasible, cytoreduction to the least possible residual tumor should be attempted, as each incremental decrease in residual disease below 1 cm may be associated with an incremental improvement in overall survival.[28] Currently, the longest reported median survival time in any phase III trial of advanced ovarian cancer was seen in optimally debulked patients with ≤ 1 cm residual disease who went on to receive intraperitoneal
Further investigation is urgently needed to preoperatively identify those patients who are most likely to benefit from cytoreductive surgery. Refining the criteria for patient selection would decrease the frequency of suboptimal debulking and potentially avoid unnecessary postoperative morbidity.

**TABLE 5**

Subsets of Patients Who May Benefit Most From Neoadjuvant Chemotherapy

NACT may be the best choice of treatment for several types of patients (Table 5). Following three courses of chemotherapy, about half of those undergoing interval debulking surgery can be completely resected.[30] However, there is still no compelling evidence that NACT prior to debulking surgery is a superior strategy for all patients with advanced disease.[43] In addition, there are no compelling advantages in quality of life during treatment or in postoperative morbidity or mortality.[30] Thus, the majority of gynecologic oncologists within the United States continue to employ NACT sparingly.[37]

Secondary debulking surgery is an option for selected patients with recurrent platinum-sensitive ovarian cancer. Prolonged survival is most likely to be associated with complete resection of disease. However, because of the wide spectrum of relapsed disease patterns, proportionally few women undergo a second debulking operation. As of the July 2011 semi-annual GOG meeting, less than 20% of patients with platinum-sensitive recurrent ovarian cancer who were enrolled in GOG protocol #213 were considered to be surgical candidates. Further tertiary, or even quaternary, debulking procedures may be reasonable to consider for highly selected patients in some circumstances.[44] The emerging era of personalized medicine is likely to have a dramatic impact on the management of advanced ovarian cancer. Inherently, it makes little sense to treat all patients diagnosed with this genetically heterogeneous disease using a single approach. In the future, pretreatment molecular profiling may be able to identify subsets of patients who are most likely to benefit from primary debulking.[45] Future trials must resolve the important question of how to triage patients to the appropriate sequence of surgery and chemotherapy. We hope that this strategy is "where we are going" in the management of advanced ovarian cancer.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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