Primary Cytoreductive Surgery for Advanced Ovarian Cancer: Is it the Past, Present, or Future?

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Abstract: Ovarian cancer accounts for more deaths in the United States than all other gynecologic malignancies combined. This is largely due to the fact that no effective screening test has been identified thus far to facilitate early detection. As a result, two-thirds of women continue to be diagnosed with advanced stage III or IV disease. Historically, the standard of care has consisted of primary cytoreductive surgery—with an operative goal of achieving an optimal result with minimal residual disease—followed by adjuvant, platinum-based chemotherapy. However, data suggesting comparable efficacy of neoadjuvant chemotherapy and interval debulking has recently challenged this conventional dogma. The current decision-making on how to initially treat women with newly diagnosed advanced ovarian cancer has become increasingly controversial. This article focuses on whether primary cytoreductive surgery should remain the preferred method of management, or whether it is time for it to be superseded by neoadjuvant chemotherapy.

Introduction

In the United States, nearly 22,000 newly diagnosed cases of ovarian cancer are estimated for 2011, along with an estimated 15,500 deaths. Ovarian cancer is the ninth leading cause of cancer in women, and the fifth leading cause of all cancer-related deaths.[1] Sex cord–stromal tumors and malignant ovarian germ cell tumors are relatively rare, and principles of debulking surgery do not necessarily apply. The subject of this review is epithelial ovarian carcinoma, which comprises 90–95% of all new diagnoses.

One in 78 American women (1.3%) will be diagnosed with ovarian cancer in their lifetime. The infrequency of this disease is a major reason why early detection has been largely unsuccessful in the general population. Only 1 out of 2,500 postmenopausal women will develop ovarian cancer annually, and there is an even less frequent occurrence in premenopausal patients. Recently, 2 large studies have explored the feasibility of screening in the slightly higher risk postmenopausal population. Between 2001 and 2005, the United Kingdom Collaborative Trial of Ovarian

Cancer Screening (UKCTOCS) randomly assigned a total of 202,638 women between ages 50–74 years to the following: no treatment, annual CA125 screening (interpreted using a risk of ovarian cancer algorithm [ROCA]) with transvaginal sonography (TVS) scan as a second-line test, or annual screening with TVS alone. ROCA-directed screening was superior, with 89.5% sensitivity and 99.8% specificity. Additionally, the positive predictive value of 35.1% was more than 10-fold higher than the observed rate of 2.8% using annual TVS. At present, the UKCTOCS data are not yet mature enough to determine the effect of ROCA-directed screening on mortality.[2] However, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial recently reported the effect on mortality using a different ovarian cancer screening strategy. From 1993–2001, this study randomly assigned 78,216 women ages 55–74 years to undergo either annual screening or usual care at 10 sites across the United States. Simultaneous screening with CA125 and TVS did not result in reduced ovarian cancer mortality when compared with usual care.[3] As these 2 trials illustrate, there is currently no proof that routine screening in either the general or high-risk populations with any modality decreases mortality.[4] Furthermore, diagnostic evaluation of a positive screening test result that is not malignant (false-positive) has been associated with unintended complications.[3]

Ovarian cancer typically does not present with acute or dramatic findings. Instead, symptoms tend to be vague and include bloating, pelvic or abdominal pain, early satiety, and frequent urination. Patients and their healthcare providers often attribute such nonspecific changes to menopause, aging, dietary indiscretions, stress, or functional bowel problems. Women may be referred to diagnostic colonoscopy, then medically managed for indigestion, irritable bowel syndrome, or other presumed ailments, oftentimes without ever having a complete gynecologic examination.[5] Substantial delays prior to diagnosis are very common, often until an abdominal-pelvic computed tomography (CT) scan is indicative of metastatic disease. As a result, two-thirds of women will present with a pelvic mass, ascites, and carcinomatosis.

Even after the diagnosis is suspected, a substantial number of patients do not receive an appropriate sequence of surgery and chemotherapy.[6,7] Instead, the majority are managed by care providers who may be unfamiliar with the expected, and commonly dramatic, initial response of ovarian cancer to aggressive treatment, despite widespread intra-abdominal metastases.[6,7] In the United States and Europe, a large proportion of primary ovarian cancer surgery is performed by low-volume surgeons at low-volume community hospitals.[8,9] Patients may present with obstructive symptoms, undergo a diverting colostomy, and then be treated with a limited duration of single-agent palliative chemotherapy, or worse, be directed to hospice. However, patients treated at a hospital that performs at least 20 ovarian cancer surgeries per year have a superior outcome.[10] One reason for this observation is that higher volume centers are more likely to provide access to subspecialty consultation. When a gynecologic oncologist is involved, patients more frequently receive the standard of care, and overall survival outcome is demonstrably improved.[11] Accordingly, these patients are less likely to be treated with surgery alone, and also less frequently receive neoadjuvant chemotherapy.[10] Unfortunately, fewer than half of newly diagnosed ovarian cancer patients will be cared for by a gynecologic oncologist.[8,12]

Cancer treatment that involves removal of large intra-abdominal tumors is an easy concept for patients and their families to understand. Several supportive, mostly theoretical, additional arguments have been proposed to justify the biologic plausibility of debulking (Table 1).[13] However, the actual clinical benefits of cytoreductive surgery have been harder to prove prospectively. Within the broader field of oncology, the aggressive surgical approach to widely metastatic disease is rather unique to ovarian cancer. The majority of clinicians believe that patients with advanced epithelial ovarian cancer do benefit from one maximal debulking attempt; however, the timing of the procedure and what defines success has become increasingly controversial.

Primary Cytoreductive Surgery

Joe V. Meigs, MD, a gynecologic surgeon at Massachusetts General Hospital, initially described ovarian tumor debulking in 1934.[14] Over the next few decades, the concept did not gain wide acceptance, mainly due to a general lack of effective chemotherapeutic agents to use after surgery. The clinical benefit of debulking was first demonstrated in the mid-1970s, when platinum drugs were also emerging. Quickly thereafter, an

Table 1. Theoretical Arguments for Debulking Surgery[13]

- Removing large necrotic masses promotes drug delivery to smaller tumors with good blood supply
- Removing resistant clones decreases the likelihood of early onset drug resistance
- Tiny implants have a higher growth fraction that should be more chemosensitive
- Removing cancer in specific locations, such as tumors causing a bowel obstruction, improves the patient's nutritional and immunologic status

aggressive surgical attempt became commonplace.[15] Case series and other retrospective data rapidly accrued to establish primary cytoreductive surgery as the de facto treatment of choice.[16,17]

At a minimum, the operation involves removal of the uterus, cervix, omentum, and bilateral adnexa. Due to local ovarian tumor extension, ancillary procedures such as rectosigmoid colectomy or en bloc resection to incorporate surrounding peritoneum are frequently required to adequately debulk the pelvis.[18] The vast majority of patients will also have "caking" of the distal omentum, necessitating removal (Figure 1).

Successful cytoreductive surgery depends on numerous factors, including patient selection, tumor location, surgeon aggressiveness, and expertise. To achieve a survival benefit, an optimal result was initially defined as leaving no tumors in situ that individually measured more than 2 cm in size.[19] For purposes of uniformity, the Gynecologic Oncology Group (GOG) redefined optimal debulking as residual implants up to 1 cm.[20] For many years, this more stringent criterion has served as the benchmark of success. However, skeptics of debulking postulated that the utilization of platinum drugs was the primary reason for improved patient outcomes. Furthermore, debulking surgery was hypothesized to simply be an indirect measure of tumor biology. In order to better evaluate the relative effect of primary cytoreductive surgery during the platinum era of the 1980s and 1990s, Bristow and associates performed a meta-analysis of 6,885 stage III/IV ovarian cancer patients.[21] Of the included studies, 95% defined an optimal result as no residual disease greater than 1 or 2 cm. According to these criteria, 42% of patients underwent optimal debulking (range, 0–100%). When controlling for the effects of all other measured variables, the percent undergoing maximal cytoreductive surgery to achieve minimal residual disease was observed to be the strongest predictor of survival time. Of particular interest is that the improvement was shown to be linear, with each 10% increase in percent optimal outcome being associated with a 5.5% increase in median survival time.[21]

Extensive upper abdominal disease is often the limiting factor determining whether the patient can be optimally debulked to minimal residual disease. Not every gynecologic oncologist has sufficient training, experience, or comfort level to perform "ultra-radical" procedures, such as liver resection, splenectomy (Figure 2), or full-thickness diaphragmatic resection.[22,23] However, a surgeon's experience and tendency to employ ultra-radical procedures is correlated to his or her success rates of optimal cytoreductive surgery.[24] Patients referred to specialized centers where such debulking techniques are commonly performed consistently have higher rates of optimal debulking, with an acceptable small increase in additional major morbidity.[25] Several institutions have successfully revised their surgical paradigm to a more aggressive philosophy incorporating ultra-radical techniques, and reported survival rates to improve accordingly.[26-29]

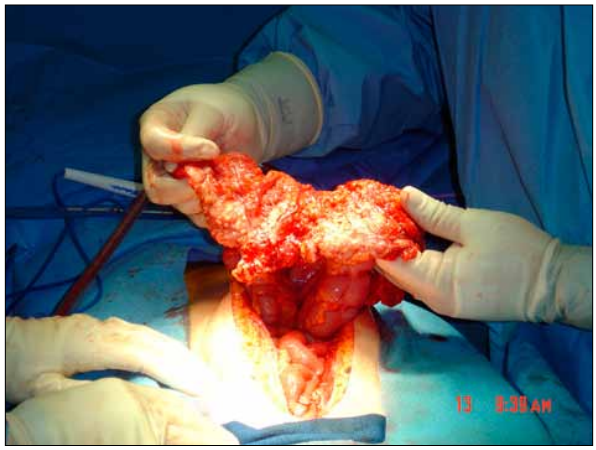

Figure 1. Omental caking with tumor in close proximity to the transverse colon.

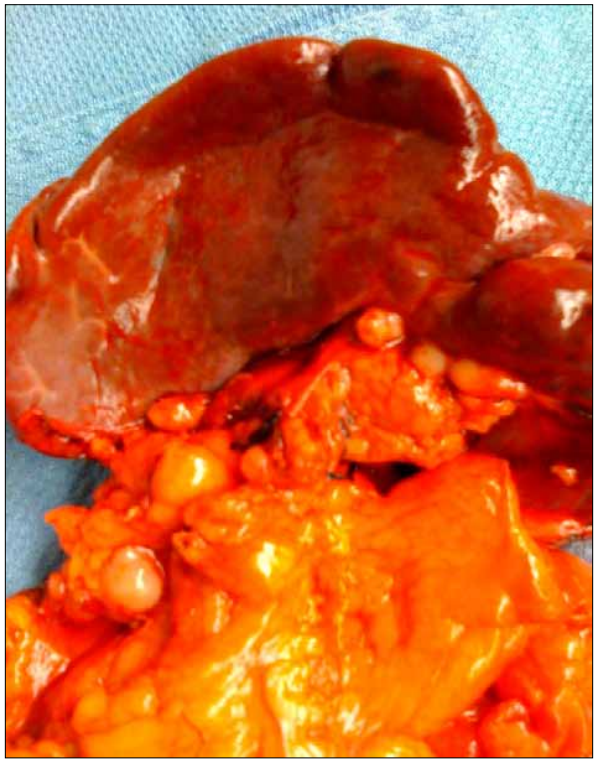

Figure 2. En bloc splenectomy with distal omentectomy demonstrating several macroscopic tumor implants.

Accumulated evidence supports the hypothesis that a surgeon's technical proficiency when performing primary debulking does meaningfully contribute to a better patient outcome rather than just indirectly reflecting an ill-defined, intrinsic feature of the cancer that makes the tumor implants easier to remove.[30,31] A surgeon's willingness to perform ultra-radical procedures also allows more patients to benefit from the proven advantages of intraperitoneal (IP) chemotherapy. Primary cytoreductive surgery achieving an optimal result (≤1 cm residual disease), followed by IP platinum-based chemotherapy, has a median overall survival of 66 months; this is the longest duration ever reported in a phase III study.[32] The level of success achieved in this GOG trial (protocol #172) is currently the gold standard for comparisons of any other sequence of treatment.

One valid criticism of cytoreductive surgery concerns the biased, subjective assessment of gross residual disease by the gynecologic oncologist at the completion of the operation. Due to tissue induration, inadequate exploration, or other factors, inaccurate assessments of residual tumor size occur frequently.[33] Perhaps due to the inability to reliably quantify the remaining disease, a recent subanalysis of accumulated data from several prospective GOG trials demonstrated that patients with 0.1–1.0 cm of residual disease had only marginally improved overall survival compared to patients with greater than 1 cm residual disease for stage III ovarian cancer, and no improvement was seen in those with stage IV disease. In fact, dramatic survival benefit was shown only in patients with complete resection to no residual disease.[34,35] Based on these findings and other similar reports (Table 2), there is a growing consensus that optimal cytoreduction should be defined using this even more stringent criterion of no gross residual disease.[25,36-38] Elevating the threshold for what constitutes successful debulking accordingly decreases the proportion of patients with stage III or stage IV ovarian cancer in which complete resection can be accomplished. Although complete resection is often not feasible, maximal cytoreduction to leave as little residual tumor as possible should always be the focus of aggressive surgical efforts, as each incremental decrease in residual disease below 1 cm may be associated with an incremental improvement in overall survival.[36]

Even when it is successful, the obvious disadvantage of aggressive 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 even postponed indefinitely.[37,38] Women who are ages 75 years or older are especially at risk for significant perioperative morbidity and 30-day mortality.[39,40] Although some centers have reported success using laparoscopy to assess the likelihood of optimal cytoreduction, the stark reality is that it remains difficult to consistently know in advance when a debulking attempt will be unsuccessful.[41] When an optimal resection is not feasible, the surgical effort should be limited in scope to avoid unnecessary excessive postoperative morbidity. Rather than performing an extensive tumor resection of questionable benefit, the maximal debulking attempt may best be postponed until later in the treatment course after initiation of chemotherapy, when the patient's performance status is typically improved.

Neoadjuvant Chemotherapy

Some ovarian cancer patients can be too medically ill to initially undergo any type of abdominal operation, whereas others have disease that is clearly too extensive to be resected even by an experienced ovarian cancer surgical team. A combination of astute clinical assessment and modern preoperative imaging can identify most of these patients.[42] In such circumstances, neoadjuvant chemotherapy is routinely used, ideally after the diagnosis has been confirmed by CT-guided biopsy, or at least paracentesis that is supported by an appropriate tumor marker profile.[38] After 3 or 4 courses of treatment, the feasibility of surgery can be reassessed. In some series, neoadjuvant chemotherapy followed by interval debulking surgery (IDS) has demonstrated comparable survival outcomes to those reported after primary surgery. Fewer radical procedures may be required, and the rate of optimal debulking is often reported to be higher. In addition, patients may experience decreased blood loss, decreased length of inpatient hospitalization, and less morbidity.[43,44]

Table 2. Median Overall Survival of Advanced Ovarian Cancer Patients Undergoing Primary Cytoreductive Surgery (months)

Residual Disease	Stage IIB–IV[25]	Stage III[34]	Stage IIIC[36]	Stage IIIC–IV[38]	Stage IV[35]	Stage IV[37]
Microscopic	73+	72	106	45	64	72
0.1–1.0 cm	37	42	59	32	29	32
>1 cm	31	35	33	25	31	20

As a result, neoadjuvant chemotherapy followed by IDS has been associated with improved overall perioperative outcomes in many retrospective case series. However, when compared to primary surgery and adjuvant chemotherapy, as observed in a study from MD Anderson Cancer Center, neoadjuvant chemotherapy-IDS also required an extended number of courses of chemotherapy (9 cycles vs 6 cycles), and prolonged overall treatment time (223 days vs 151 days) to achieve clinical remission.[45]

Delaying surgery may provide more knowledge about the biologic behavior of the tumor, potentially enabling treatment to be tailored more effectively in some instances.[42] For example, approximately 10% of patients receiving neoadjuvant chemotherapy develop platinum-refractory disease and end up avoiding any surgical attempt.[37,38] IDS may also be postponed beyond 3 or 4 courses of platinum-based neoadjuvant chemotherapy. Performing IDS after 6 cycles of neoadjuvant chemotherapy has been shown to yield even higher complete resection rates without appearing to adversely affect overall survival. However, this sequence will need to be prospectively evaluated in further trials before more widespread acceptance is earned.[46]

Despite many potential advantages, some data suggest that using neoadjuvant chemotherapy in lieu of primary debulking may be associated with an inferior overall survival.[47,48] Direct comparisons have historically been difficult to perform. In 1986, the GOG and a separate collaborative group in the Netherlands each opened randomized phase III trials to test the hypothesis that primary debulking was superior to neoadjuvant chemotherapy in advanced ovarian cancer. Both studies were closed due to poor accrual. One prevailing opinion at the time was that clinicians did not want to subject their patients to neoadjuvant chemotherapy treatment that they perceived was substandard. 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 European Organisation for Research and Treatment of Cancer (EORTC) were first presented in October 2008, and subsequently published in September 2010.[38] The data have reopened the debate about how to best initially treat women with advanced ovarian cancer. In the study, 670 stage IIIC and stage IV patients were randomized to primary debulking surgery versus neoadjuvant chemotherapy. After 3 courses of platinum-based treatment, neoadjuvant chemotherapy patients who demonstrated a response underwent IDS. The authors reported a similar median overall survival of 29–30 months for each 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 appear to matter. Based on the authors' interpretation of their data, neoadjuvant chemotherapy-IDS was not inferior to primary surgery.

Despite these findings, most gynecologic oncologists in the United States utilize neoadjuvant chemotherapy for fewer than 10% of advanced ovarian cancers.[49] Some European gynecologic oncologists have openly questioned what kind of evidence would be needed to convince their American colleagues about the superiority of the neoadjuvant chemotherapy approach.[50] At least 2 criticisms of the EORTC trial have been suggested as reasons why the results may not be applicable in the United States. First, the duration of patient survival in the study was shorter than many expected. The median survival (29–30 months) was less than half that reported for optimally debulked stage III patients receiving postoperative IP chemotherapy (66 months).[32] Additionally, only 42% of the primary debulking operations achieved an optimal result, with no greater than 1 cm of residual disease. Since expert centers often report an optimal result in at least 75% of patients, it is feasible to postulate that a more aggressive initial attempt might have led to a better outcome for the group randomized to surgery. Recently, Chi and colleagues analyzed the outcomes of patients treated with primary debulking surgery at Memorial Sloan-Kettering Cancer Center during the same time period as the EORTC trial, and with identical study inclusion criteria. Optimal cytoreduction (≤1 cm of residual disease) was achieved in 71% of patients, and median overall survival was 50 months.[51]

A prospective phase III trial conducted within the United States will ultimately need to be performed in order to sway opinion and markedly change the practice of gynecologic oncologists in this country. The GOG has approved the concept (#OVM1005), but opening, accruing, completing, and analyzing this trial will take years. In the meantime, the controversy will persist, and individual patterns of care will continue.

Conclusion

Improving the quality of care for patients with advanced ovarian cancer requires increased recognition of the clinical importance of incorporating a gynecologic oncologist in initial treatment planning. The goal of debulking surgery should be complete resection to no macroscopic disease, rather than leaving residual tumors of 1–2 cm. Primary cytoreductive surgery that achieves a complete resection has consistently demonstrated the best long-term outcome of any treatment strategy in stage III ovarian cancer. Since ultraradical procedures are routinely required, centers embracing an aggressive surgical paradigm have the highest success rates. Consistent referral of patients with apparent advanced ovarian cancer to gynecologic oncologists at expert centers may

Table 3. Characteristics of Patients Who May Benefit Most from Neoadjuvant Chemotherapy

Stage IV disease (likelihood of complete resection <10%)
Stage III disease that is too extensive to be optimally debulked based on clinical assessment and/or imaging modalities
Performance status too poor to undergo an attempt at surgical debulking
No access to an experienced ovarian cancer surgical team

be the best means currently available for improving overall survival.[21] When not feasible, cytoreduction to achieve as minimal residual disease as possible should be attempted using surgical judgment to balance potential perioperative risks and benefits, as each incremental decrease in residual disease below 1 cm may be associated with an improvement in overall survival.[36] Further studies are urgently needed to preoperatively identify patients 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.

Currently, the longest reported median survival in any phase III trial of advanced ovarian cancer includes optimally debulked patients with up to 1 cm residual disease who go on to receive IP chemotherapy.[32] The survival benefit associated with IP chemotherapy after optimal upfront surgery does not necessarily translate to the neoadjuvant setting. Neoadjuvant chemotherapy may be the best choice of treatment for several types of patients (Table 3). Delaying surgery also provides more knowledge about the biologic behavior of the tumor, and this can be used to tailor treatment more effectively.[42] Following 3 courses of chemotherapy, about half of those undergoing interval debulking surgery can be completely resected.[38] However, there is still no compelling evidence that neoadjuvant chemotherapy prior to debulking surgery is a superior strategy for all patients with advanced disease.[52] In addition, there are no compelling advantages in quality of life during treatment, or in postoperative morbidity or mortality.[38] Thus, the majority of gynecologic oncologists within the United States continue to employ neoadjuvant chemotherapy sparingly.[49] Future trials will aim to resolve the important question of how to triage patients to the appropriate sequence of surgery and chemotherapy.

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