Review

Primary debulking surgery for advanced ovarian cancer: Are you a believer or a dissenter?

John O. Schorge a,*, Rachel M. Clark a, Susanna I. Lee b, Richard T. Penson c

a Vincent Gynecologic Oncology Service, Massachusetts General Hospital, USA
b Division of Abdominal Imaging, Massachusetts General Hospital, USA
c Division of Medical Gynecologic Oncology, Gillette Center for Gynecologic Oncology, Massachusetts General Hospital, USA

HIGHLIGHTS

• The goal of primary debulking surgery should be the complete resection of all macroscopic disease.
• Neoadjuvant chemotherapy has an emerging role in the treatment of selected patients.
• Preoperative innovations under investigation are aimed at better triaging women to upfront surgery or chemotherapy.

ARTICLE INFO

Article history:
Received 8 September 2014
Accepted 7 October 2014
Available online 12 October 2014

Keywords:
Primary debulking surgery
Neoadjuvant chemotherapy
Advanced ovarian cancer

ABSTRACT

Nothing stirs the collective soul of primary debulking surgery (PDS) advocates like hard data suggesting equivalent outcomes of neoadjuvant chemotherapy (NAC). These opposing views have even metaphorically come to blows at the highly entertaining “SGO Fight Night” that took place during the 2008 Annual Meeting on Women’s Cancer, replete with teams supporting each of the would-be gladiators. Decades of retrospective data supporting the clinical benefit of PDS has recently been challenged by the publication in 2010 of a randomized phase III trial conducted in Europe supporting the clinical efficacy of NAC. Naturally, a firestorm of criticism among believers ensued, yet practice patterns within the United States did slowly change, suggesting an emerging block of dissenters. Another randomized phase III European trial, as presented in abstract form in 2013, showed similar findings. Few other topics within the field of gynecologic oncology have participants so entrenched in the “corners” of their existing practice patterns. This review attempts to consolidate the current evidence supporting both sides so that the patient can be declared the winner.

© 2014 Elsevier Inc. All rights reserved.
Introduction

The consistent inability to reliably detect ovarian cancer before widespread metastases has proven to be logistically problematic and a source of ongoing disappointment. Unfortunately, routine screening has not been shown to meaningfully improve early detection, nor reduce mortality in either the high-risk or general populations [1–3]. The U.S. Preventive Services Task Force currently recommends against screening given the scant evidence for any benefit, but consistently observed harms from unnecessary interventions [4]. Symptoms of ovarian cancer tend to be vague and are often attributed to menopause, stress, or functional bowel problems. Substantial delays prior to diagnosis are very common, often until an abdominal-pelvic computed tomography (CT) scan is obtained. As a result, two-thirds of women who are newly diagnosed with invasive epithelial ovarian cancer still present, as they always have, with stage III–IV disease typically characterized by ascites, carcinomatosis and omental caking.

Advanced ovarian cancer is a heterogeneous disease requiring a disciplined sequence of treatment to consistently achieve the best outcomes. No two clinical presentations are quite the same, nor would two different clinicians necessarily be in sync on every patient. Whether to start with an operation, or platinum-based therapy, is not always obvious, no matter what the pre-existing biases. Primary debulking surgery (PDS) requires knowledge of the disease process, mastery of a wide spectrum of different procedures, and the willingness to manage complex postoperative sequelae. Neoadjuvant chemotherapy (NAC) appears to involve less short-term morbidity, and has demonstrated equivalent efficacy, at least in one published phase III trial [5]. Clinical teams are charged with the challenging task of striking the perfect balance between being appropriately aggressive and trying to avoid unnecessary morbidity. The most strident advocates of either PDS or NAC will have treated selected patients with the alternative on at least some occasions. This intriguing frequency of crossover is well-known, but not often stated.

Due to the complexities of providing longitudinal care for patients with ovarian cancer, better outcomes are reported when a subspecialist is involved [6,7]. Unfortunately, fewer than half of patients in the United States and Europe will have that opportunity [8]. Instead, the majority are managed by physicians not necessarily intimately familiar with the interplay between medical and surgical management. However, maximizing overall survival depends on the precise coordination of both forms of treatment at a center with expertise. PDS and NAC each have their believers and dissenters. Recently, decades of retrospective data supporting the former has collided with phase III data supporting the latter position. Apropos to the boxing analogy, we cannot retreat into our corner at this point, but must be willing to go the distance with the best currently available evidence for the benefit of all women diagnosed with advanced ovarian cancer. Furthermore, we must look for ways to improve our treatment paradigms.

Primary debulking surgery

Joe V. Meigs, a gynecologic surgeon at the Massachusetts General Hospital (Fig. 1), initially described ovarian tumor debulking in 1934 [9]. The initial intent was to enhance the effects of radiation therapy in an era before modern chemotherapeutics. However, due to limited clinical benefit, the concept did not really gain traction until the mid-70s when platinum drugs were emerging. Griffiths’ (Fig. 2) landmark study appeared to conclusively demonstrate the inverse relationship between residual tumor diameter and patient survival [10]. Case series and other retrospective data rapidly accrued thereafter to establish PDS as the de facto standard of care for advanced ovarian cancer [11–13].

Removal of the uterus, ovaries and any other intra-abdominal tumors as part of ovarian cancer treatment is an easy concept for patients and their families to understand. Often there is an unrealistic assumption that taking out the offending site of origin will stop the spread of cancer, and that peritoneal dissemination includes a finite number of tumors that once removed, will not return. The actual clinical benefits of debulking have been harder to prove in a rigorous fashion. Within the broader field of oncology, this type of aggressive surgical approach to widely metastatic disease has some parallels, especially when complete cytoreduction can be achieved [14–17].

Several supportive, but mostly theoretical, arguments have been proposed to justify the biological plausibility of debulking (Table 1) [18,19]. Disseminated ovarian cancers, like other solid tumors, are postulated to contain a small subpopulation of highly specialized cells with self-renewal capacity and the potential to reconstitute the entire cellular heterogeneity of a tumor. These ovarian cancer stem cells are thought to be responsible for tumor initiation, maintenance and growth. Presumably, ineffective targeting of this cell population is responsible for the therapeutic failures and tumor recurrences frequently observed [20,21]. The elimination of these chemoresistant cells, removal of the supportive tumor microenvironment, and potential for improved drug delivery, are, in theory at least, other benefits of surgical cytoreduction. Additionally, removal of bulk disease should reduce the number of...
chemotherapy-treated cancer cells that will undergo spontaneous mutations to drug-resistant phenotypes [22].

PDS is a technically challenging endeavor for a number of different reasons. Tumor-related sequelae such as symptomatic pleural effusions or hypoalbuminemia, especially when accompanied by co-existing health problems, often impact the ability to recover from any major surgical procedure. Within the peritoneal cavity, anatomical landmarks are often encased by tumor or otherwise obliterated. Routinely, radical pelvic dissection, bowel resection, and aggressive upper abdominal surgery are necessary to achieve an optimal result [23]. Sound clinical judgment is required in order to be appropriately aggressive, without inducing a cascade of potentially disastrous complications. Despite the accumulated evidence supporting the importance of PDS, 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 [24,25]. While patients definitely do appear to benefit from one maximal debulking attempt, the timing of the operation and what defines success have become increasingly controversial.

Proficient cytoreduction 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 individually measuring more than 2 cm in size [26]. For purposes of uniformity, the Gynecologic Oncology Group (GOG) re-defined optimal debulking as residual implants ≤ 1 cm [27]. For some decades, this criterion served as the benchmark of success. Patients undergoing PDS who were rendered optimal (≤ 1 cm residual disease), followed by intraperitoneal (IP) platinum-based chemotherapy were shown to have a median overall survival of 66 months — the longest duration ever reported in a phase III study [28]. The clinical outcomes achieved in this GOG trial still serve as the benchmark for comparisons with any other sequence of treatment.

Yet one valid criticism of cytoreductive surgery is the biased, subjective assessment of gross residual disease by the surgeon at the completion of the operation. Due to tissue induration, inadequate exploration, radiologist over-estimation, or other factors, inaccuracies of residual tumor size are common [29,30]. Perhaps due to the inability to reliably quantify the remaining disease, a recent sub-analysis of accumulated data from several prospective GOG trials demonstrated that patients with 0.1 to 1.0 cm residual disease had only marginally improved overall survival compared to patients with > 1 cm residual disease for stage III ovarian cancer. In fact, dramatic survival benefit was only achieved with complete resection to microscopic residual disease [31]. Based on these findings and other similar reports, there is a growing consensus that optimal cytoreduction should be defined using a more stringent criterion. Thus, the current goal of PDS is to achieve complete resection with no residual disease [32].

Raising the bar for surgical success accordingly decreases the proportion of patients with advanced ovarian cancer in which this redefined optimal result can be accomplished, unless there is a change in practice. For stage IIIc diseases, rates of complete resection predominantly range from 15 to 30%. However, the clinical benefits appear substantial when it can be achieved (Table 2) [33–35]. Within the last decade, multiple institutions have demonstrated the ability to revise their surgical paradigm in order to safely debulk to no residual disease at a rate that approaches or exceeds 50% [36–38]. Broader incorporation of these types of surgical improvement programs could significantly improve outcomes. In a meta-analysis of 18 studies involving 13,257 patients, Chang et al. observed that each 10% increase in the proportion undergoing complete cytoreduction was associated with a 2.3-month increase in cohort median survival. Additionally, for each 10% increase in the proportion receiving IP chemotherapy, there was a 3.9-month increase in median cohort survival time [39]. Recently, Rosen et al. reported an astonishing seven-year survival rate of 90% in women undergoing PDS with no residual disease who subsequently received IP treatment [40]. All attempts should be made to achieve complete (hereafter defined as optimal in this review) resection, as these patients, when treated with adjuvant platinum-based IP chemotherapy have survival measures that exceed any rates previously seen in this population [41].

However, despite the subjective nature of classifying residual disease, there is evidence to support minimizing the amount of remaining tumor as much as possible. Chi et al. analyzed a prospective database for outcomes of 465 women with stage IIIc ovarian cancer who underwent PDS. They observed a median overall survival of 33–34 months for those with > 1 cm residual disease, 48 months with 0.6–1.0 cm residual,

<table>
<thead>
<tr>
<th>Study</th>
<th>Residual disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microscopic</td>
</tr>
<tr>
<td>Aletti [23]</td>
<td>&gt;84</td>
</tr>
<tr>
<td>Chang [34]</td>
<td>86</td>
</tr>
<tr>
<td>Chi [35]</td>
<td>106</td>
</tr>
</tbody>
</table>
66 months for those with ≤0.5 cm, and 106 months for patients with no gross residual disease [35]. Additionally, in a Cochrane Database review of 11 retrospective studies, “near optimal” patients with <1 cm residual disease collectively had better outcomes than “suboptimal” cases with residual disease >1 cm [42].

Occasionally, a gynecologist planning to remove an adnexal mass or a general surgeon performing abdominal surgery for presumed bowel obstruction unexpectedly encounters widespread intra-abdominal disease. These advanced ovarian cancer patients who are unintentionally taken for surgery typically do not get a maximal cytoreductive effort, but are oftentimes referred postoperatively. Fortunately, upfront re-operation before the start of chemotherapy should still be feasible, and successful, in more than half of patients with incomplete primary surgery elsewhere [43].

If it were possible to perform PDS and consistently achieve no residual disease with limited postoperative complications, then we all would be believers in this strategy. Despite attempts to develop such a model – predicting successful surgery with minimal morbidity – nothing yet has proven reproducible in a prospectively validated manner [44,45]. At present, the reality is that most patients will have some level of remaining tumor, and many will derive limited clinical benefit. Additionally, PDS may result in a prolonged postoperative recovery that is fraught with complications: an observation frequently made by dissenters to the upfront surgery paradigm. All too often, the initiation of chemotherapy may be delayed, or worse, postponed indefinitely.

**Neoadjuvant chemotherapy (NAC)**

Some patients are clearly too medically ill to initially undergo any type of upfront abdominal operation, whereas others have disease that is too extensive to be resected even by an experienced ovarian cancer surgical team. In these circumstances, NAC is routinely used after the diagnosis has been confirmed. Core biopsy of the primary tumor or one of the metastases is the gold standard to prove the existence of a disseminated ovarian carcinoma. Cytological diagnosis by fine needle aspiration may also be acceptable if the CA125/CEA ratio is ≥25 (as defined in trials) [46]. Following three to four courses of treatment, the feasibility of surgery can be reassessed. In some retrospective series, NAC followed by interval debulking has demonstrated comparable survival outcomes to those reported for primary surgery [47–50]. Fewer radical procedures may be required, the rate of achieving minimal residual disease may be higher, and patients may experience less morbidity. Six cycles of NAC prior to surgery are another less commonly used option. In 82 patients treated with this extended regimen, the rate of complete resection to no residual disease was 63.7%, and 23.1% were found to have had a clinical complete response [51]. However, a meta-analysis of 81 cohorts of 6885 patients with stage III or IV ovarian cancer suggested that NAC in lieu of PDS is associated with an inferior overall survival [52]. Direct comparison has historically been difficult to perform.

Unfortunately, preoperative CA125 levels, imaging tests and physical examinations all have limitations in consistently identifying which patients can be optimally debulked to no residual disease by a gynecologic oncologist. Invariably, the final determination cannot be made until abdominal exploration. When it is clinically evident during surgery that achieving <1 cm is not feasible, great discretion is required to confirm the diagnosis, but not provoke unnecessary complications that could delay subsequent therapy.

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 multicenter trial conducted in Europe demonstrated a 6-month median survival advantage in patients who were re-explored after three cycles of chemotherapy [53]. In contrast, no survival advantage was demonstrated when a similar study was conducted in the United States [54]. These seemingly conflicting reports are most easily explained by clarifying who performed the first surgery. In the US trial, virtually all patients had their initial attempt by a gynecologic oncologist, unlike the European study where relatively few had their first surgery performed by a subspecialist. Therefore, interval debulking appears to yield benefit only among the patients whose primary surgery was not performed by a gynecologic oncologist, if the first try was not intended as a maximal resection of all gross disease, or if no upfront surgery was performed at all [55].

**PDS v NAC: phase III trials**

In 1986, the GOG and separately a collaborative group in the Netherlands each opened randomized phase III trials to test the hypothesis that primary debulking was superior to NAC 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 ‘substandard’ NAC treatment. Until recently, the presumed benefits of primary surgical cytoreduction in advanced ovarian cancer had not been rigorously tested. The results of the randomized European Organization for Research and Treatment of Cancer (EORTC protocol # 55971) phase III trial were first presented in October 2008 and subsequently published in September 2010. The data has fostered debate of how best to initially treat women with advanced ovarian cancer. In the study, 670 patients were randomized to PDS versus NAC. After three courses of platinum-based treatment, the 80% of NAC patients who demonstrated a response underwent interval debulking. The authors reported a median overall survival of 29 to 30 months, regardless of the initial 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. Based on the authors’ interpretation of their data, NAC and interval debulking was the preferred treatment [5].

Despite these findings, the Society of Gynecologic Oncology members queried in 2010 largely remained unconvinced. Of respondents to a survey sent to the membership, most use NAC in less than 10% of advanced stage ovarian cancer cases [56]. In light of the phase III data, some European gynecologic oncologists have openly questioned what kind of evidence would be needed to convince their US colleagues about the superiority of the NAC approach [57]. At least two criticisms of the 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 expected. The median survival (29 to 30 months) was less than half that reported for optimally debulked stage III patients receiving postoperative intraperitoneal chemotherapy (66 months) [28]. Additionally, only 42% of those patients randomized to PDS had ≤1 cm of residual disease.

Since expert centers in the United States often report achieving cytoreduction to ≤1 cm of residual disease at least 75% of the time, it is feasible to think that a more aggressive initial attempt might have led to a better outcome for the group randomized to surgery. Chi et al. analyzed the outcomes of patients treated with PDS at the Memorial Sloan-Kettering Cancer Center during the same time period in which the EORTC trial was conducted, using identical inclusion criteria. Of 316 eligible patients, 285 (90%) underwent PDS. In 203 patients (71%), ≤1 cm of residual disease was achieved with an overall median overall survival of 50 months [58]. The long-term outcomes were intriguing, but whether this was a fair comparison has been debated [59].

A second recently presented study is also of interest. The Medical Research Council (MRC) CHEMotherapy OR Upfront Surgery (CHORUS) trial is a phase III, non-inferiority randomized controlled study conducted in the United Kingdom and New Zealand. Five hundred fifty-two newly diagnosed advanced ovarian cancer patients with suspected stages III–IV ovarian cancer were enrolled between March 2004 and August 2010. Women were randomized to undergo PDS followed by 6 cycles of chemotherapy, or NAC with interval debulking surgery.
after 3 cycles, followed by completion chemotherapy. The primary outcome was overall survival, with secondary outcomes of toxicity and quality of life. Complete resection was achieved in 16% of the PDS arm versus 40% in the NAC arm. Grades 3–4 postoperative adverse events (24% v 14%) and death (5.5% v 0.5%) within 28 days of surgery were both more common in the PDS group. Median overall survival was comparable between the two arms: 22.8 months for the PDS arm and 24.5 months for the NAC group [60]. Peer-review of the manuscript is eagerly awaited as it represents another meaningful contribution to the literature on this topic.

Ultimately, a prospective phase III trial conducted within the United States will need to be performed to sway opinion and markedly change the practice of gynecologic oncologists in this country. Unfortunately, recent attempts through the GOG or with industry support have not yet been successful in launching. Meantime, the controversy will persist and individual patterns of care will continue. PDS is certainly the standard of care for patients with stage IIIA and IIIB ovarian cancer. PDS is also favored for those with IIIC disease, in the absence of evidence for unresectability or poor performance status. The treatment of stage IV is typically individualized in current patterns of practice, but NAC is a reasonable alternative [61].

Special circumstances

The elderly

Since the likelihood of a woman developing ovarian cancer increases with every decade, and the population is living longer than ever before, it stands to reason that more and more women will be diagnosed later in life. The precise meaning of the term ‘elderly’ is somewhat fluid, occasionally referring to those as young as 65 years of age, but in some studies defined as 75 years and older. While increasing age as a stand-alone variable should not immediately lead to a more palliative approach, it is a relevant factor as almost half of ovarian cancer patients diagnosed in the United States each year will be at least 65 years of age. Though the exact reasons are usually difficult to separate out and tend to be multifactorial, increasing age does adversely impact survival. As a group, elderly patients with ovarian cancer are less likely to receive care with a gynecologic oncologist, or to undergo PDS followed by adjuvant chemotherapy [62,63]. Some of the differences in patterns of care are likely driven by medical co-morbidities, well-meaning physician bias and/or individual quality of life choices.

Increasing age and co-morbid conditions are risk factors for surgical morbidity and mortality, but the interactions have not been rigorously analyzed. Several studies have emphasized that elderly patients are able to tolerate an aggressive approach with relatively few complications, when adjusted for performance status. Langstraat et al. reviewed the Mayo experience of 280 consecutive patients ≥65 years with stage IIIC or IV ovarian cancer treated over a 10-year period. A significant number of elderly women were able to undergo PDS and adjuvant chemotherapy. However, median overall survival still decreased with increasing age and the impact of residual disease was greater on older patients. In addition, 37.5% of patients ≥75 years had significant perioperative morbidity [64]. Glasgow et al. performed a retrospective cohort study of women ≥70 years with stage IIIC or IV disease treated at Yale, and observed that the 42 NAC patients had similar outcomes, but significantly reduced perioperative morbidity compared to 62 women who underwent PDS [65]. Worley et al. reviewed the outcome of 165 patients aged ≥70 years at their institution. Median overall survival was similar between the 125 women who underwent PDS, compared to the 40 receiving NAC, but readmission rates within 30 days of surgery was dramatically higher in the PDS cohort (17.6% v 2.5%) [66].

These single institution studies highlight the caution that is indicated for elderly women, especially in the presence of other significant co-morbidities. Thrall et al. analyzed the Surveillance, Epidemiology and End Results (SEER) data -base to identify a cohort of 5475 women aged ≥65 years who had PDS for stage III or IV epithelial ovarian cancer between 1995 and 2005. The overall 30-day mortality was a sobering 8.2%. Advancing age, increasing stage, and increasing co-morbidity score were all associated with an increase in 30-day mortality [67]. Wright et al. analyzed the SEER-Medicare database to identify women aged ≥65 with stages II–IV ovarian cancer who survived at least 6 months from the date of diagnosis. A total of 9587 patients were identified who received treatment from 1991 to 2007. Interestingly, the use of primary surgery decreased from 63.2% to 49.5% over time. In addition, overall survival with NAC did not differ from PDS in this older population [68]. In an analysis of 28,651 women undergoing surgery for ovarian cancer from 1998 to 2007 using the Nationwide Inpatient Sample, complication rates increased with age from 17.1% in those <50 years of age to 31.5% in those ≥80. Morbidity was observed to be greatest in the elderly, where the effects of age and the number of radical procedures performed had an additive effect on complication rates [69]. En masse, the data suggests that NAC will likely continue to have a more prominent role in the elderly. When complete cytoreduction is not feasible during PDS, the operation should be limited in scope to avoid unnecessary postoperative morbidity as ultra-radical procedures can be especially poorly tolerated in this population.

Obesity

The epidemic of obesity taking place in the United States and throughout much of the world is increasingly going to impact the treatment of ovarian cancer. While studies exploring the association between obesity and ovarian cancer survival have yielded conflicting results [70–74], using a body mass index (BMI) of 30 kg/m² as the tipping point for the definition of obesity hardly seems to reflect reality. In the current vernacular, 40 is the new 30, at least as far as the aging process goes, and we should be able to comfortably extrapolate that also to BMI. Kumar et al. analyzed the Mayo experience with 620 stages IIIC–IV patients who underwent PDS between 2003 and 2011, divided into three groups according to BMI. Women with a BMI of ≥40 were found to have substantially higher rates of severe 30-day postoperative morbidity and 90-day mortality after PDS. Although the high BMI group had limited numbers of patients, there did not appear to be deficits in achieving optimal cytoreduction, nor did it impact long-term oncologic outcomes [75]. It seems obvious enough that the likelihood of postoperative complications is demonstrably higher when performing PDS in the morbidly obese population. Even though the ability to achieve complete cytoreduction would seem to be in jeopardy with increasing body size, current data do not bear this out, perhaps due to a mitigating effect of excess body weight on tumor biology [76]. Matthews et al. observed that survival rates were similar between obese and non-obese patients when the amount of residual disease was the same [77]. Regardless, there is a price to be paid for aggressive PDS in the morbidly obese, though NAC too has potential limitations in this population.

Wright et al. observed that obese patients treated with chemotherapy on a GOG protocol experienced substantially less toxicity than normal weight women. Substandard drug dosing was thought to be causative [78]. In an analysis of the Australian Ovarian Cancer Study of 333 patients, obese women were significantly more likely to have received <85% of relative dose intensity of carboplatin, leading to worse outcomes [79]. Appropriate dosing for obese patients with ovarian cancer is a must, whether as NAC or given as postoperative adjuvant treatment. When they undergo effective and receive appropriate doses of chemotherapy, obese patients do not have a poorer prognosis [80].

Stage IV disease

Roughly one-third of patients with advanced ovarian cancer will have stage IV disease at the time of their diagnosis [81]. This designation is widely believed to be associated with a more aggressive tumor biology having significant implications on surgical outcome and response to
chemotherapy. Accordingly, the likelihood of achieving complete cytoreduction at the time of PDS is particularly dismal (Table 3) [82–86]. Furthermore, Winters et al. retrospectively reviewed 360 stage IV patients treated on phase III GOG protocols and did not observe a benefit with 0.1 to 1.0 cm residual disease versus those with 1.1 to 5.0 cm residual. They concluded that ultra-radical procedures might best be targeted to those selected patients in whom microscopic residual disease is achievable [86]. Based on the available data, this would seem to apply to less than 1 in 10 patients.

Van Meurs et al. used data from the EORTC 55971 trial to report that patients with stage IV disease and large (defined as > 45 mm) metastatic tumors treated with NAC had demonstrably higher survival, compared to an attempt at PDS followed by postoperative chemotherapy [87]. In addition, NAC patients with stage IV disease who subsequently undergo interval debulking surgery appear to have less peri-operative morbidity, a higher likelihood of complete resection and shorter hospital stay [88]. In the EORTC trial, 10% of patients randomized to NAC never had a cytoreductive attempt [5]. Another advantage of NAC in this high-risk population appears to be the ability to better triage only responding patients to interval debulking surgery. Among this subset, aggressive cytoreduction has been shown to be beneficial [89].

While historically the stage IV subcategory represented a range of clinical findings lumped together, since January 2014 these have been separated out to better reflect the disease processes [90]. It will be of interest to see whether having stage IVA or IVB disease will have implications on the success of upfront treatment. Based on current available evidence, the ability to achieve complete resection to no residual disease is so limited, that upfront surgery should be limited to very select patients, while the majority should be treated with NAC.

**Clinical innovations**

**Preoperative imaging**

The ability to reliably identify patients most likely to benefit from PDS based on imaging findings has proven to be an immense challenge. Bristow et al. retrospectively analyzed preoperative CT scans in a blinded fashion and correlated them with surgical outcome to develop a predictive index model [91]. In a similar study, Dowdy et al. identified only diffuse peritoneal thickening and large volume ascites as findings associated with a low rate of optimal debulking [92]. These attempts, and others like them, have not led to a paradigm shift, mainly due to variations of image interpretation and surgical expertise across institutions. In a multi-institutional reciprocal validation study, high accuracy rates of CT predictors could not be confirmed [93]. Suidan et al. have recently reported the results of a prospective, non-randomized two-center trial of 669 patients from 2001 to 2012 that underwent PDS for stages III–IV ovarian, fallopian tube, and peritoneal cancer. Based on three clinical and six radiologic criteria (Table 4, Fig. 3), they developed a predictive model in which the suboptimal rate was directly proportional to the predictive value score [94]. These findings have yet to be validated more broadly.

![Fig. 3](image-url) Ovarian carcinosarcoma with peritoneal carcinomatosis. Coronal image from an abdominal-pelvic CT with oral and intravenous contrast shows a 17-cm primary right adnexal tumor (star). Bulky tumor in the lesser sac (arrow) would suggest the inability to perform complete cytoreductive surgery.

![Table 3](image-url) Success rates of primary debulking surgery in stage IV ovarian cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Residual disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microscopic</td>
</tr>
<tr>
<td>Aletti [76]</td>
<td>6%</td>
</tr>
<tr>
<td>Bristow [77]</td>
<td>–</td>
</tr>
<tr>
<td>Rauh-Hain [78]</td>
<td>8%</td>
</tr>
<tr>
<td>Trope [79]</td>
<td>14%</td>
</tr>
<tr>
<td>Winter [80]</td>
<td>8%</td>
</tr>
</tbody>
</table>

* American Society of Anesthesiologists Physical Status classification system.

**Table 4** Suidan et al. criteria associated with suboptimal primary cytoreductive surgery.
While there is as yet no clear consensus on the criteria for resectable peritoneal lesions, radiologic imaging serves as an important roadmap for treatment planning. The American College of Radiology’s Appropriateness Criteria consensus recommendations currently rate abdominal–pelvic CT as the modality of choice for pre-treatment evaluation of ovarian cancer patients [100]. Chest CT is also indicated should the chest radiograph prove abnormal. Accurate interpretation requires radiologist expertise in complex intra-abdominal anatomy, and clinical dialogue with a gynecologic oncologist having familiarity with specific disease sites that are likely to present particular difficulties with regard to surgical access and technique [101]. Although CT is at present the most predictive procedure, it is not in and of itself accurate enough to consistently guide clinical management.

**Minimally invasive surgery**

The inherent limitations in accurately correlating imaging findings for a disease with varying levels of intraperitoneal surface implant dissemination detected at surgery has led to evolving paradigms where preoperative laparoscopic evaluation of disease is used to help triage patients toward PDS or NAC. In theory, this approach would avoid unnecessarily morbid, suboptimal laparotomies that unduly lengthen the time of treatment and increase overall costs. Several prospective and retrospective studies have investigated the use of laparoscopy to predict the outcome of debulking surgery. In a pilot study of patients undergoing laparoscopy followed by standard laparotomy, Fagotti et al. observed that optimal debulking was achievable in 87% of cases selected as being completely resectable by explorative laparoscopy [102]. With this promising preliminary data, a laparoscopy-based quantitative predictive model (predictive index value [PIV]) was devised to provide an objective score of intraperitoneal disease spread (Table 5). The PIV has subsequently undergone initial testing and validation as a triage tool [103,104]. To minimize the chances of inappropriately failing to perform PDS, the best PIV cutoff was noted to be ≥8, corresponding to a positive predictive value of 100%, or a zero percent chance of complete resection among these investigators [105].

Fagotti et al. subsequently reported on 300 consecutive patients who underwent staging laparoscopy. Importantly, none had complications related to the procedure. Based on high tumor load (PIV ≥ 8), 152 (50.7%) went on to receive NAC and 57.5% had no residual disease at the time of interval debulking. Of the 148 who underwent PDS, 62.1% had complete resection. The authors concluded that this minimally invasive strategy may help to meaningfully individualize treatment, while avoiding unnecessary open surgery and its sequelae [106]. Vizzelli et al. also reported 348 consecutive advanced ovarian cancer patients who underwent preoperative laparoscopic evaluation. All study women received a PIV score and were stratified into three groups based on volume of disease. In a multivariate analysis, tumor load stratified by PIV was found to be independently associated with overall survival, along with the amount of residual disease and performance status [107].

In a multicenter trial (Olympia-MITO 13) to prospectively evaluate the accuracy and reproducibility of staging laparoscopy at different satellite centers, 168 patients underwent PIV scoring. Following a short intensive training period, the technique was shown to be an accurate and reliable assessment of intraperitoneal diffusion of disease in advanced ovarian cancer patients [108]. The LapOvCa-trial is a randomized multicenter trial including all gynecologic oncology centers in the Netherlands and their affiliated hospitals. The purpose of this ongoing study is to investigate whether laparoscopy is cost-effective in predicting which patients will benefit from PDS and which patients should be treated by NAC and interval surgery instead [109].

Whether the PIV score will be readily adaptable to gynecologic oncologists in the United States remains an open question. Nick et al. recently presented the triage algorithm modified from Fagotti that is currently under investigation at the MD Anderson Cancer Center. Of the 33 patients who underwent laparoscopy, none had an intraoperative complication, and 19 (58%) who had a PIV score ≥8 subsequently underwent PDS. By the use of this approach, their rate of achieving complete resection improved from a historical rate of 44% to 84% [110].

**Table 5**

<table>
<thead>
<tr>
<th>Fagotti laparoscopic predictive index value (PIV) score.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omental cake</td>
</tr>
<tr>
<td>Peritoneal/diaphragmatic carcinomatosis</td>
</tr>
<tr>
<td>Mesenteric retraction</td>
</tr>
<tr>
<td>Bowel/stomach infiltration</td>
</tr>
<tr>
<td>Spleen/liver superficial metastasis</td>
</tr>
</tbody>
</table>

Each positive evaluation receives a score of 2.
However, more data is needed. In a Cochrane Database review of seven studies reporting on six cohorts, laparoscopy identified a broad range (27–64%) of patients with too extensive disease to warrant laparotomy and correspondingly between 36–73% having disease suitable for PDS. Laparoscopy is a promising tool with minimal complications, but the limited number of studies and unproven reproducibility at present do not allow firm conclusions to be drawn from this data as yet [111].

Ultra-radical surgery

Extensive upper abdominal disease is often the limiting factor determining whether a patient with advanced ovarian cancer can be optimally debulked to no residual disease. While tumor in this location is strongly indicative of aggressive tumor biology, a surgeon’s experience and willingness to employ ultra-radical procedures is correlated with success in achieving complete resection [112,113]. Not every gynecologic oncologist is comfortable routinely performing liver resection, splenectomy, or diaphragmatic resection, and complications may not be trivial. However, patients referred to specialized centers where such radical procedures are commonly performed may anticipate higher rates of optimal debulking and improved survival, without necessarily leading to increased major morbidity [114]. Several institutions incorporating ultra-radical techniques have reported survival rates to improve accordingly [36–38]. Although it is still unclear what impact ultra-radical techniques have on quality of life and morbidity, the limited available evidence suggests a measured improvement in survival [115]. One common theme for safely expanding the ability to completely resect advanced ovarian cancer is the willingness to incorporate a multidisciplinary surgical team, as needed, to facilitate debulking outside of the provider’s typical comfort zone. In addition, having tertiary care resources to manage the wide variety of possible postoperative complications is critically important. Complex patients warrant treatment in a specialized center.

Synopsis

Current surgical management of ovarian cancer requires excellent clinical judgment and technical mastery of a wide array of procedures. Involvement of a gynecologic oncologist to oversee patient care has proven to improve outcomes. Complete resection of all macroscopic disease at PDS has been shown to be the single most important independent prognostic factor in advanced ovarian cancer. Therefore, when deciding on PDS there should be a reasonable chance of leaving no residual tumor or at least substantial cytoreduction to ≤ 1 cm at the time of surgery [46].

The ability to clinically gauge those most likely to be completely cytoreduced and thereby effectively triage patients toward PDS or NAC involves a complex interplay of numerous factors, including imaging findings, physical examination, existing medical co-morbidities, and the expertise of the surgical team. No single individual has the capacity to make the right call in every circumstance, and even if it were the case, it would not necessarily benefit patients outside of his/her purview. We advocate a team approach to interpret available information and allow the patient to make an informed decision toward initial therapy. To that end, a consistent preoperative treatment planning conference is ideal, with multi-disciplinary attendance, consistent imaging review and ongoing reassessment of outcome measures. In this way, co-existing factors such as elderly age, morbid obesity or stage IV disease extension can all be taken into account (Tables 6 and 7).

Further modification of current imaging techniques is unlikely to substantially improve the triage of patients upfront. The promising work on laparoscopic scoring needs to be replicated in the United States with reassuring survival outcomes, otherwise it is unlikely to be widely incorporated. Ultimately, any and all of these preoperative methods to predict complete resection are still intimately tied to the surgeon’s ability to translate them into a successful outcome. While several institutions have demonstrated improvement in rates of achieving optimal debulking by incorporation of ultra-radical techniques, it is difficult to conceive of pushing the surgical limits much beyond that.

Future strategies

Rather than refining subjective clinical assessments such as imaging or laparoscopy, it is likely that a reproducible genomics-based model will be necessary to effectively triage patients to initial therapy. Preliminary data on a signature that predicts the success of debulking has been proposed, but much additional work is needed before this becomes a reality [116]. It seems feasible, at least in theory, that molecular analysis of a percutaneous core biopsy might ultimately be the most cost-effective method for determining when or if a patient should go to surgery, and what type of targeted therapy is likely to be most efficacious.

At a more basic level, just having access to subspecialty care continues to be a significant problem. It is an unfortunate reality that geographic proximity to a high-volume hospital and travel distance to receive treatment are independent predictors of guideline-adherent care for advanced ovarian cancer. Such barriers disproportionately affect racial minorities and women of low socio-economic status [117]. Networks that are able to successfully integrate ovarian cancer treatment across tertiary and community hospitals need to be promoted and expanded so that all women diagnosed can receive the same level of care. Management of advanced ovarian cancer consistently requires a complex, multidisciplinary team to achieve the best outcomes. Whenever feasible, patients should be encouraged to seek treatment at these expert centers.

Whether you are a believer or a dissenter of PDS, we have very limited data to interpret. Only a randomized phase III trial of PDS versus NAC performed in the United States with impressive rates of optimal cytoreduction will be definitive. We should embrace this challenge of constructing a well-designed definitive study and vigorously support those, such as Dennis Chi, who are trying to find a way to fund such a trial. It is telling that without substantial pharmaceutical industry support of an agent or device, there is an impasse in conducting a trial to answer this basic question.

Finally, since surgical paradigms have been shown to improve with sustained effort, more transparency per provider or per institution would be helpful in measuring where there are lessons to be learned or improvements to be incorporated. Hopefully, the newly launched SGO Clinical Outcomes Registry will provide this type of detailed data. In the meantime, the gynecologic oncology community is charged with identifying further evidence-based refinements in the approach to upfront treatment, continuing to train fellows in the range of procedures that may be required for primary or interval debulking surgery, and broadening the access to subspecialty care.

Table 6

| Patients who appear to benefit the most from primary debulking surgery: a proposal. |
|---------------------------------|-------------|
| Stage IIIA or IIIB disease     | Stage IIIc disease with Fagotti laparoscopic score <8 |
| Stage IIIc disease with promising multidisciplinary imaging review at ‘expert’ center routinely able to incorporate ultra-radical procedures as appropriate | Stage IIIc disease that is too extensive to be optimally debulked based on imaging or laparoscopic scoring |
| Stage IV disease (likelihood of complete resection <10%) | Performance status too poor to undergo an attempt at surgical debulking |
| No access to an experienced ovarian cancer surgical team | The elderly or morbidly obese when ultra-radical procedures appear necessary |

Table 7

| Patients who appear to benefit the most from neoadjuvant chemotherapy: a proposal. |
|---------------------------------|-------------|
| Stage IIIC disease that is too extensive to be optimally debulked based on imaging or laparoscopic scoring |
| Stage IV disease (likelihood of complete resection <10%) |
| Performance status too poor to undergo an attempt at surgical debulking |
| No access to an experienced ovarian cancer surgical team |
| The elderly or morbidly obese when ultra-radical procedures appear necessary |
For the foreseeable future, most women will continue to be diagnosed with ovarian cancer after it has already spread extensively within the peritoneal cavity. The debate on efficacy of PDS versus NAC appears to be still in the early rounds. None of us should prematurely declare our side the winner, nor throw in the towel on this metaphorical boxing match, but instead work together to fight the common enemy. It is incumbent upon all of us to continue exploring ways to establish a structured, consistent, transparent approach to the best initial management of this disease. Hopefully, that is something that we can all believe in, without discretion.

Conflict of interest statement
The authors have no financial disclosures to report at this time.

References


