Neoadjuvant Chemotherapy for Advanced Epithelial Ovarian Cancer

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Keywords
Advanced epithelial ovarian cancer, cytoreductive surgery, neoadjuvant chemotherapy

Abstract: The historical standard treatment paradigm for advanced epithelial ovarian cancer is surgical staging followed by adjuvant platinum- and taxane-based chemotherapy. It is well established that patients gain a survival advantage when optimal surgical debulking is achieved; surgical intervention that leaves bulky disease does not confer the same advantage. Thus, when optimal cytoreductive surgery is not possible or would lead to excessive morbidity, neoadjuvant chemotherapy followed by interval cytoreductive surgery is employed. There currently is no externally validated predictive model or consensus regarding which patients should be selected for primary debulking surgery vs neoadjuvant chemotherapy. This article reviews the current literature on the use of neoadjuvant chemotherapy as a treatment strategy for patients with advanced epithelial ovarian cancer.

Introduction

Epithelial ovarian cancer (EOC) remains the deadliest gynecologic cancer, with an estimated 21,290 new cases and 14,180 deaths[1] in 2015. The behavior of fallopian tube and primary peritoneal carcinomas is clinically similar to that of EOC, with approximately two-thirds of patients having advanced-stage disease at the time of diagnosis. These diseases are therefore included under the heading of EOC for the purposes of this review.[1,2]

Current guidelines for the primary treatment of advanced EOC recommend cytoreductive surgical staging followed by adjuvant platinum- and taxane-based chemotherapy.[2] Primary debulking surgery (PDS), or cytoreductive surgery, became accepted as the standard of care for up-front treatment after 1975, when a landmark study by Griffiths demonstrated an inverse relationship between postsurgical residual tumor and patient survival.[3,4] Several subsequent studies have demonstrated the same survival benefit since that time, with the definition of optimal cytoreduction ranging from a tumor diameter of less than 2 cm to no evidence of disease.[4-7] It is also important to note that these same studies have shown that

when the residual tumor diameter is larger than 2 cm, there is little to no impact on survival.[4,5,8] Despite data supporting the survival benefit of PDS, there remains a population of patients for whom cytoreductive surgery is not feasible or who would be subjected to significant morbidity for optimal debulking of tumor to be achieved. In these patients, neoadjuvant chemotherapy (NACT), or the administration of chemotherapy before cytoreductive surgery, is recommended.[2] Unfortunately, triage methods and the clinical benefit of PDS vs that of NACT remain vigorously debated.

Goals of Multidisciplinary Treatment

Advanced EOC generally is associated with a large tumor burden. Unlike metastatic disease in other malignancies, however, metastatic disease in EOC often is limited to the abdominal cavity and is amenable to PDS.[9] The goal of PDS in advanced EOC is to achieve optimal cytoreduction of the tumor. The definition of optimal cytoreduction has evolved over time, from residual disease less than 2 cm in diameter at the completion of surgery to residual disease less than 1 cm in diameter, the definition currently accepted by the Society of Gynecologic Oncology.[2,4-7] The more contemporary view of optimal cytoreduction is that there be no evidence of disease or no residual tumor at the completion of debulking surgery.[2,6] Arguments in favor of PDS include alleviating symptoms; promoting drug delivery to small, well-vascularized tumors; decreasing drug resistance through the removal of resistant clones; altering the tumor microenvironment; and increasing sensitivity to chemotherapy by limiting disease to small implants with a rapid growth fraction.[9,10] Additionally, when optimal PDS has been achieved, patients are considered eligible for adjuvant intraperitoneal chemotherapy, which to date has been associated with the longest median survival (65.6 months) of any ovarian cancer regimen.[2,11]

When optimal PDS is not feasible, NACT is an alternative option that has the potential to decrease the burden of disease and increase the likelihood of complete tumor resection at the time of definitive surgery, which is known as interval cytoreductive surgery (ICS).[2] Current guidelines recommend that all patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease that is potentially resectable undergo cytoreductive surgery during their course of treatment.[2] This includes patients who have received NACT and those with incomplete staging. For patients receiving NACT, ICS preferably is performed after 3 cycles of chemotherapy but may be done after 4 to 6 cycles based on clinical judgment.[2]

Proponents of NACT report that it decreases the morbidity of surgery, increases the rate of optimal cytoreduction, shortens the postoperative hospital stay, improves patient quality of life during treatment, and does not compromise overall survival.[8,10,12,13] An additional benefit of NACT is that it allows an assessment of the effectiveness of chemotherapy, given that patients whose disease does not respond to chemotherapy have proven chemoresistance and therefore are at high risk for recurrence.[9]

Pretreatment Evaluation

There is a lack of consensus on which patients with advanced EOC should be considered candidates for PDS vs NACT, and currently no externally validated model exists to predict which patients will have significant morbidity from surgery or will have optimal cytoreductive surgery.[14-16] The decision to perform PDS vs NACT generally is based on the patient's preference, clinical presentation, and disease burden. It is important to note that the availability of a surgeon with specialized training in gynecologic oncology has been associated with a survival benefit in patients who have advanced EOC.[17] Therefore, the standard of care is for a gynecologic oncologist or another surgeon with training in radical cytoreductive cancer surgery to be involved in determining whether a patient's disease is resectable at the time of PDS.[2]

The patient's age, performance status, nutritional status, and medical comorbidities are independent prognostic factors that should be considered when a decision regarding primary treatment is made, although the independent prognostic value of each of these is not entirely clear.[18-22] Although older age appears to be linked to poorer survival in advanced EOC, it is well-known that older women often are treated less aggressively with either surgery or chemotherapy, which might account for the association.[20-22] It is also important to note that the presence of comorbid conditions correlates poorly with functional status, and therefore the heterogeneity of the EOC population should be considered when it is being determined whether a patient should receive PDS or NACT.[20,22,23]

In order to counsel patients preoperatively about the potential morbidity of surgery, predictive models incorporating patient characteristics and laboratory values have been reported, although none has been validated. One such model is that proposed by Barber and colleagues, which takes age, ascites, white race, smoking status, preoperative serum creatinine, platelets, white blood cell count, hematocrit, and albumin into consideration (Table).[24]

The other factors to be considered in making primary treatment choices are the extent of disease at diagnosis and the potential for optimal surgical cytoreduction. The best method to assess both these factors remains under investigation. The reliability of the currently recommended evaluation for identifying patients with advanced EOC

Table. Predictive Models of Suboptimal Cytoreductive Surgery and Surgical Complications

Authors	Significant Predictive Factors
Barber et al[24]	*Clinical:* Age, ascites, white race, smoking status *Laboratory:* Serum creatinine, platelets, white blood cell count, hematocrit, albumin
Bristow et al[28]	*Clinical:* Gynecologic Oncology Group performance status ≥2 *Radiologic:* Peritoneal thickening; peritoneal implants ≥2 cm; small-bowel mesenteric disease ≥2 cm; large-bowel mesenteric disease ≥2 cm; omental extension to stomach, spleen, or lesser sac; extension to pelvic side wall or parametrium, or hydroureter; large-volume ascites; suprarenal para-aortic lymph nodes; diaphragmatic or lung base disease ≥2 cm; inguinal canal disease or lymph nodes ≥2 cm; liver lesion ≥2 cm on surface or parenchymal lesion of any size; porta hepatis or gallbladder fossa involvement; infrarenal para-aortic lymph nodes ≥2 cm
Dowdy et al[29]	*Radiologic:* Diffuse peritoneal thickening
Suidan et al[32]	*Clinical:* Age ≥ 60 years, American Society of Anesthesiologists physical status classification score of 3 or 4 *Laboratory:* CA-125 ≥500 U/mL *Radiologic:* Suprarenal para-aortic lymph nodes, diffuse bowel wall thickening, perisplenic lesions, small-bowel mesenteric involvement, root of superior mesenteric artery involvement, lesions in lesser sac
Stashwick et al[33]	*Laboratory:* CA-125 ≥500 U/mL, albumin *Radiologic:* Diffuse peritoneal studding, para-aortic retroperitoneal lymphadenopathy >2 cm, mesenteric disease, splenic disease
Fagotti et al[37]	*Laparoscopic:* Ovarian mass (unilateral or bilateral), omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, bowel infiltration, stomach infiltration, liver metastasis

CA-125, cancer antigen 125.

in whom PDS will be optimal is limited. The current standard evaluation involves using a combination of the cancer antigen 125 (CA-125) level and the imaging and physical examination findings.[2,10] A CA-125 level above 500 U/mL has been described by researchers as predictive of suboptimal cytoreduction; however, more recent reports from centers with expertise in aggressive debulking of EOC indicate that elevated CA-125 is a marker of the presence of upper abdominal disease rather than a reliable predictor of outcomes.[25-27] Preoperative imaging has yet to yield more consistent prediction. In a retrospective review published in 2000, Bristow and colleagues described a model that predicted optimal cytoreduction in advanced EOC with 93% accuracy based on the identification of 13 computed tomography (CT) findings and performance status.[28] In another retrospective review, Dowdy and colleagues reported that diffuse peritoneal thickening on CT scan, defined as greater than 4 mm, was the only independent predictor of the potential for suboptimal cytoreduction.[29] Validation studies of these and other models using CT predictors of suboptimal cytoreduction have found poor reproducibility, leading to the conclusion that preoperative CT predictors should be used with caution.[30,31] Suidan and colleagues have proposed a predictive model of optimal cytoreduction that uses 3 clinical factors and 6 radiologic findings, but its reproducibility has yet to be proven.[32] The same holds true for the surgical risk score developed by Stashwick and colleagues to predict suboptimal debulking and the risk for major perioperative complications, which also has not been externally validated.[33]

In addition to preoperative models using the CA-125 level, CT findings, and/or clinical factors, some models use diagnostic laparoscopy to predict the results of cytoreductive surgical efforts. Proponents of this approach report that laparoscopy can spare patients laparotomy and makes it possible to procure tissue for a diagnosis and molecular analysis. In addition, patients in whom optimal cytoreduction is deemed unlikely do not have to recover from laparotomy before starting NACT.[34] Vergote and colleagues were among the first to report using open laparoscopy to determine the use of NACT or PDS in patients with radiologic evidence of metastatic disease.[35] Subsequently, in 2004, Fagotti and colleagues published their pilot study looking at the role of diagnostic laparoscopy in assessing the chance of optimal cytoreduction. They found that diagnostic laparoscopy was equivalent to laparotomy for this purpose.[36] After the pilot study, Fagotti and colleagues developed a predictive index value, called the Fagotti score, that used laparoscopic findings to more reproducibly determine who should go on to PDS vs NACT.[37] Olympia-MITO 13 (Validation of a Laparoscopic Score to Predict the Chance of Optimal Cytoreduction in Advanced Ovarian Cancer Patients) was a prospective multicenter trial designed to verify the reproducibility of this score. It was found that all but one of the 10 satellite centers involved in the study were able to determine the predictive index value with 80% or greater accuracy.[38] A recent Cochrane review of the 7 studies that used diagnostic laparoscopy prediction models points out that the application of various criteria

results in no patients inappropriately undergoing exploration, but no currently published model entirely eliminates unsuccessful primary laparotomy.[39] Ongoing evaluations at US cancer centers of the incorporation of laparoscopic scoring systems into algorithms that can be used to identify patients in whom complete resection is likely at the time of PDS demonstrate feasibility and hold promise that higher rates of complete surgical resection of disease can be achieved.[40]

Consistent among the predictive models using radiologic findings and laparoscopy are the criteria used for unresectable disease: involvement of the porta hepatis, bowel mesentery, liver parenchyma, or suprarenal para-aortic lymph nodes; involvement of more than just the tail of the pancreas; stomach infiltration; and extensive small-bowel involvement.[28-30,32,34,37,38] Optimal cytoreduction is unlikely to be achieved in patients with these findings at the time of PDS, and therefore they should be considered candidates for NACT with ICS.

Survival Outcomes

Perhaps the most important issue in the debate over PDS vs NACT in advanced EOC is the survival associated with each treatment modality. Numerous published studies have addressed this question, including case-control series, prospective randomized trials, systematic reviews, and meta-analyses.

Survival data for patients with advanced EOC who received NACT with or without ICS were first widely reported in the 1990s because it was used in women who underwent suboptimal PDS followed by platinum-based chemotherapy, and in patients deemed unfit to undergo surgery. In 1990, a group at Yale published their experience of using chemotherapy as initial treatment in 17 patients with advanced EOC.[41] Median survival was 15 months, and the survival curves were the same as those for 2 subsets of patients with stage III or stage IV EOC treated at Yale with PDS followed by chemotherapy during the same interval. In 1991, Jacobs and colleagues published a retrospective case-control study on their experience of using NACT with ICS at the University of Texas MD Anderson Cancer Center.[42] The study group consisted of 22 patients who were referred to the center with stage III or stage IV EOC after laparotomy and biopsy; they received 2 to 4 cycles of chemotherapy followed by ICS and further chemotherapy. The study group was compared with 2 control groups, the first of which consisted of patients who underwent suboptimal debulking followed by platinum-based chemotherapy. The second control group included patients who were referred with stage III or stage IV EOC after laparotomy and biopsy and who received PDS followed by chemotherapy after referral. No statistically significant difference was found in the median survival of the 3 groups (16, 19.3, and 18 months, respectively). This finding led the authors to conclude that patients with bulky residual disease have a uniformly poor prognosis. Since that time, other institutional series and retrospective reviews have been published, with similar findings. These publications have noted that NACT does not compromise the survival of women with advanced EOC and have emphasized the need for prospective randomized trials.[35,43-45]

The mid-1990s saw the publication of the first prospective randomized trials looking at NACT and ICS and their impact on survival. In 1994, Redman and colleagues reported on 79 patients who underwent suboptimal PDS and were then randomly assigned to receive platinum-based chemotherapy alone or platinum-based chemotherapy followed by debulking surgery if a chemotherapy response was demonstrated.[46] In this study, no statistically significant difference was found between the median survival of the chemotherapy-only arm (12 months) and the median survival of the patients who received chemotherapy and surgical debulking (15 months); however, the authors commented that this study may have been too small to detect such a difference. In 1995, Van der Burg and colleagues published the findings of the European Organisation for Research and Treatment of Cancer (EORTC)-55865 study (Phase III Study for the Treatment of Ovarian Cancer FIGO Stages IIB and C, III and IV), which evaluated the same concept.[47] In this trial, 319 women with advanced EOC and residual tumor larger than 1 cm in diameter after PDS were given 3 cycles of platinum-based chemotherapy. Those without progressive disease were then randomly assigned either to surgical cytoreduction or to no further surgery followed by 3 more cycles of chemotherapy. There was a statistically significant difference between the groups in median overall survival, which was 26 months in the patients receiving surgical cytoreduction and 20 months in the patients who received no further surgery. Similarly, progression-free survival was longer in the surgical intervention group (18 months) than in the chemotherapy-only group (13 months). From this finding, the authors of EORTC-55865 concluded that debulking surgery significantly lengthened both overall survival and progression-free survival in patients with advanced EOC after induction chemotherapy.

The Gynecologic Oncology Group (GOG) also has published a randomized trial, protocol 152, that evaluated the role of secondary cytoreduction in patients after suboptimal debulking and chemotherapy.[48] In GOG 152, patients with FIGO stage III or stage IV EOC and residual intraperitoneal tumor larger than 1 cm in diameter received platinum and taxane chemotherapy. After their third cycle, those whose disease had not progressed and who had limited extraperitoneal disease were randomly assigned

either to further chemotherapy alone or to secondary surgical cytoreduction followed by chemotherapy. A total of 550 patients were enrolled initially, and 448 underwent randomization. The median time to progression of the surgery group did not differ significantly from that of the chemotherapy-only group (10.5 months vs 10.7 months). A nonsignificant difference also was found between the overall survival of the secondary cytoreduction group and that of the chemotherapy-alone group (33.9 months vs 33.7 months). From this result, the GOG 152 investigators concluded that secondary cytoreduction is of no benefit in patients with maximal PDS but may be of benefit in those with inadequate primary surgery. Additionally, they commented that the use of newer chemotherapeutic agents (paclitaxel and platinum) in GOG 152 vs older agents (cyclophosphamide and platinum) in EORTC-55865 may have accounted for the difference in findings.

Although the earlier trials previously described studied the feasibility and benefit of cytoreduction after chemotherapy, they did not directly seek to determine a difference in survival by comparing NACT with ICS vs PDS followed by adjuvant chemotherapy. In 2010, Vergote and colleagues published the results of the Gynecologic Cancer InterGroup study EORTC 55971 (European Organisation for Research and Treatment of Cancer Gynecological Cancer Group–National Cancer Institute of Canada Clinical Trials Group), a randomized trial comparing PDS with NACT in patients who had biopsy-proven FIGO stage IIIC or stage IV EOC.[13] In this study, 670 patients were randomly assigned either to PDS followed by adjuvant platinum-based chemotherapy or to 3 cycles of platinum-based NACT with ICS followed by at least 3 more cycles of chemotherapy. The authors found higher rates of optimal cytoreduction, defined as residual tumor diameter of less than 1 cm, with ICS after NACT than at the time of PDS (80.6% vs 41.6%). In the intent-to-treat analysis for EORTC 55971, the hazard ratio (HR) for death was 0.98 (90% CI, 0.84-1.13) and the HR for progression of disease was 1.01 (90% CI, 0.89-1.15) in the NACT group vs the PDS group. The progression-free survival was 12 months for both treatment groups, and the overall survival was 29 months for PDS and 30 months for NACT. Based on these findings, Vergote and colleagues concluded that NACT with ICS is not inferior to PDS followed by adjuvant chemotherapy in patients with bulky FIGO stage IIIC or stage IV EOC. A major criticism of EORTC 55971 was the inferiority of both progression-free survival and overall survival in comparison with outcomes during the same period in the United States, where overall survival averaged 50 months.[2,49-51] EORTC 5591 was also criticized for substandard surgery with comparatively low rates of optimal debulking, and for the presence of a selection bias toward patients with a worse prognosis.[49-52]

More recently, Kehoe and colleagues published the results of another randomized controlled trial, CHORUS (Primary Chemotherapy Versus Primary Surgery for Newly Diagnosed Advanced Ovarian Cancer).[53] CHORUS was a phase 3 noninferiority trial that randomly assigned 552 women with FIGO stage III or stage IV EOC to receive either PDS followed by 6 cycles of platinum-based chemotherapy or 3 cycles of platinum-based NACT with ICS followed by 3 more cycles of chemotherapy. The CHORUS findings were similar to those of EORTC 55971. The median overall survival was 22.6 months in the PDS group compared with 24.1 months in the NACT group. The HR for death was 0.87 in favor of NACT (95% CI, 0.72-1.05). Progression-free survival was 12 months for NACT vs 10.7 months for PDS, with the HR also favoring NACT (0.91 with a 95% CI of 0.76-1.09). In this trial, optimal cytoreduction, defined as residual tumor diameter of less than 1 cm, was achieved in 41% of the PDS group and in 73% of the NACT group. From the CHORUS results, the authors concluded that NACT with ICS was noninferior to PDS plus adjuvant chemotherapy and was associated with less surgical morbidity. The criticisms of CHORUS are similar to those of EORTC 55971 and largely centered on the possibility of substandard surgical procedures with low optimal cytoreduction rates and on a selection bias toward patients with a heavy tumor burden.[54] Given the criticisms of patient selection and surgical resection in both EORTC 55971 and CHORUS, the debate over the impact of PDS compared with NACT on overall survival and progression-free survival continues.

To date, 3 meta-analyses have addressed primary treatment in advanced EOC. The first to look specifically at survival outcomes was the one by Bristow and Chi, which included 22 articles published between 1989 and 2005 representing 835 patients with stage III and IV disease.[55] In this meta-analysis, the authors found that the median overall survival was 24.5 months and that median survival decreased with each increase in preoperative chemotherapy. Based on their meta-analysis, Bristow and Chi concluded that NACT was associated with an inferior overall survival compared with PDS. Another meta-analysis, by Kang and Nam, evaluated 21 studies conducted between 1989 and 2008 to determine whether NACT did in fact increase the rates of optimal cytoreduction.[56] In this publication, the authors concluded that NACT improved optimal cytoreduction rates and that the number of NACT cycles did not influence survival. In a more recent meta-analysis, Dai-yuan and colleagues included 2 randomized control trials that found no difference in median overall survival or progression-free survival between patients receiving PDS and those receiving NACT.[57] Systematic reviews of the literature also report the current lack of consensus on the role of NACT.[7-10,51,58-60]

Tumor Biology

When choice of primary therapy is being considered, and in future studies of the treatment of advanced EOC, it should be asked whether it is tumor biology rather than intervention that determines prognosis and survival. In 1986, Heintz and colleagues reported that cytoreduction was easier to achieve in patients with small metastases, low-grade tumors, and no ascites.[61] The idea is logical that tumors demonstrating less biologically aggressive behavior are more amenable to cytoreduction and therefore carry a more favorable prognosis. This concept was evaluated in GOG 52, which failed to prove that patients presenting with large-volume disease had the same survival as patients presenting with small-volume disease after up-front debulking surgery.[62] More recent studies have contradicted these findings, showing that residual tumor at the completion, not the initiation, of surgery is the prognostic factor.[4-7,63,64]

The same argument that tumor biology dictates prognosis can be made at the molecular level. The better a tumor cell is at evading DNA repair mechanisms, the more likely it is to continue propagating and resist treatment. Unfortunately, translational experiments thus far have failed to determine definitively if tumor biology alone determines prognosis. Some investigations find differences, whereas others find a lack of difference in gene expression profiling between patients with optimal and those with suboptimal cytoreductive surgery.[65,66] Until advances are made that allow better prediction of tumor behavior, the question of tumor biology vs intervention will remain unanswered.

Conclusions

PDS remains the standard of care in the United States for the treatment of advanced EOC. However, NACT with ICS is often employed in patients who are deemed too frail to undergo PDS or in whom optimal cytoreduction would require procedures leading to morbidity. Until methods of triaging patients and identifying tumor biology are improved, the decision to perform PDS vs NACT plus ICS remains one way in which providers may be able to alter the trajectory of patient survival in EOC.

Disclosures

Drs Hall and Dizon have no relevant disclosures to report.

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