Update on the Role of Surgery in the Management of Advanced Epithelial Ovarian Cancer

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Abstract: Surgical cytoreduction and platinum/taxane-based chemotherapy are the cornerstones of the management of advanced ovarian cancer; however, the optimal timing and order of these interventions remain a topic of debate. Interpreting the available data, specifically regarding the role of neoadjuvant chemotherapy in the primary setting and surgical cytoreduction in the recurrent setting, requires careful evaluation of surgical quality and patient selection. One tenet that has persisted throughout the historical and modern literature is the prognostic effect of the volume of residual disease after cytoreductive surgery. The goal of debulking surgery has appropriately evolved to that of the complete gross resection of all visible disease, and the repertoire of the gynecologic cancer surgeon has grown to include radical pelvic, upper abdominal, and thoracic procedures. Novel surgical techniques are under investigation, such as minimally invasive cytoreductive procedures and the intraoperative utilization of heated intraperitoneal chemotherapy. Of equal importance is a recent refocusing of attention on patient preferences and the patient's experience during treatment and recovery. In this review article, we examine the literature supporting the role of surgery in the management of advanced ovarian cancer.

Keywords
Cytoreductive surgery, debulking surgical procedures, hyperthermic intraperitoneal chemotherapy, neoadjuvant chemotherapy, ovarian cancer, patient-reported outcomes

Introduction

Worldwide, approximately 300,000 new cases of ovarian cancer are diagnosed annually, and 185,000 ovarian cancer–related deaths occur each year.[1] Surgery remains the backbone of the primary management of advanced epithelial ovarian cancer (EOC).[2] Despite a multitude of genomic and medical advances in the understanding and management of EOC over the past 20 years, the volume of residual disease after debulking surgery remains one of the most important prognostic factors for overall survival (OS).[3-6] Therefore, complete resection of all visible disease has become the goal of surgery.[7] Although the importance of a complete gross resection (CGR) is nearly universally agreed upon, the scope, timing, and philosophy regarding surgical debulking for EOC—specifically,

the roles of neoadjuvant chemotherapy (NACT) in the primary setting and secondary debulking in the recurrent setting—continue to be controversial topics in the field. In this review, we focus on the evolving role and scope of surgery in the management of ovarian cancer.

Timing of Surgery

Primary Management of Advanced EOC and the Timing of Debulking Surgery

The standard treatment of a patient with a new diagnosis of EOC consists of surgical debulking and platinum/taxane chemotherapy, possibly followed by maintenance therapy with an agent such as a poly(ADP-ribose) polymerase (PARP) inhibitor or bevacizumab. Debulking surgery can be done in the primary setting, before the administration of systemic chemotherapy, or in the interval setting, after the administration of NACT. No universally agreed-upon criteria are available to guide the choice of NACT vs primary debulking surgery (PDS), and fierce advocates for each approach continue to debate over which is preferable. To date, 4 randomized controlled trials (RCTs) have evaluated the efficacy of NACT vs PDS: 3 noninferiority trials and 1 superiority trial (Table 1). Of the published studies, 2 demonstrate noninferiority of NACT compared with PDS, in terms of progression-free survival (PFS) and OS. The first was the European Organisation for Research and Treatment of Cancer trial (EORTC 55971), published in 2010, which randomized 670 patients with stage IIIC/IV EOC to PDS followed by adjuvant chemotherapy vs NACT with interval debulking surgery (IDS).[8] The median PFS in both arms was 12 months, whereas the median OS was 29 months for PDS vs 30 months for NACT. Women who had an optimal resection (41.6% of those in the PDS arm and 80.6% of those in the NACT arm) had better survival. The second trial demonstrating noninferiority was the CHORUS study, published in 2015. This trial randomized 550 patients with suspected stage III or IV ovarian cancer in a 1:1 ratio to undergo either PDS followed by adjuvant therapy or NACT followed by IDS. The trial showed no difference in PFS (median of 10.7 months for PDS vs 12 months for NACT) or OS (median of 22.6 months for PDS vs 24.1 months for NACT).[9] The CHORUS trial demonstrated improved survival with optimal resection, the rate of which was 41% in the PDS arm and 73% in NACT arm.

The remaining 2 trials were presented at the 2018 American Society of Clinical Oncology (ASCO) annual meeting. The SCORPION trial was a randomized superiority trial comparing PDS with NACT/IDS in 171 patients who had stage IIIC/IV disease. After a median follow-up of 42 months (95% CI, 30-50 months), the trial did not show a difference in PFS between patients. who underwent PDS vs NACT (15 vs 14 months; hazard ratio [HR], 1.06; 95% CI, 0.77-1.46). NACT was not shown to be superior to PDS by these results.[10] The second trial, conducted by the Japanese Gynecologic Oncology Group (JCOG0602), was a multicenter phase 3 noninferiority trial in which 301 patients with advanced EOC were randomly assigned to PDS or NACT/IDS. This trial failed to demonstrate noninferiority of NACT. The 2 arms did not differ in median PFS (15.1 months for PDS vs 16.4 months for NACT) or median OS (49.0 months for PDS vs 44.3 months for NACT).[11,12] These trials demonstrated fewer complications in the NACT arms than in the PDS arms.[8-11]

Although these 4 randomized clinical trials are used to support the argument that NACT/IDS is comparable to PDS, concerns remain regarding the generalizability of the results to all patients in all clinical settings. One common criticism is the generally poor outcomes seen in both arms of these prospective RCTs. In the 2 published RCTs demonstrating noninferiority of NACT, the median PFS ranged from 10.7 to 12 months in the PDS arms and was 12 months in the NACT arms; median OS ranged from 22.6 to 29 months in the PDS arms and from 24.1 to 30 months in the NACT arms.[8-9] These results stand in contrast to those of multiple published prospective and retrospective studies with similar cohorts of patients that demonstrate markedly longer PFS and OS with PDS. Gynecologic Oncology Group (GOG) 172, published in 2006, was a randomized phase 3 clinical trial evaluating the use of intraperitoneal chemotherapy in patients with stage III epithelial or primary peritoneal carcinoma at the time of PDS. Patients were required to have undergone an optimal resection (residual disease ≤1 cm). In this study, PFS was 18.3 months and OS was 49.7 months.[13] Similarly, multiple single-institution studies at large, high-volume centers have reported much longer survival outcomes, such as those published by Mueller and colleagues in 2016. In this cohort of 568 patients with stage III disease, patients who underwent PDS had a median OS of 71.7 months (95% CI, 59.8 months to not reached), and in those who underwent NACT, it was 42.9 months (95% CI, 37.1-56.3 months).[14]

The results of the recently accrued TRUST trial, also known as ENGOT ov33/AGO-OVAR OP7,[15] are awaited and may help settle this debate. TRUST is a randomized controlled international multicenter trial designed to test the hypothesis that PDS is superior to IDS with respect to OS in patients who have EOC. Patients with stage IIIB-IVB EOC were enrolled. Surgical quality control was integral to the design of this trial, and participating centers had to undergo rigorous protocols, including proof of their surgical rates for achieving CGR. The trial

Table 1. Summary of the Randomized Controlled Trials Evaluating Primary Debulking Surgery vs Neoadjuvant Chemotherapy

Study, Years of Enrollment	Study Design, Site	Surgical Quality Control, Stages Included, N	Arms	CGR[a] RD, %	Optimal[b] RD, %	Median PFS, mo	Median OS, mo	Conclusions	Complications
EORTC 55971,[8] 1998-2006	Noninferiority, multiple sites in EORTC network	No, IIIC-IV, 670	PDS NACT	19.4 51.2	41.6 80.6	12 12	29 30	NACT noninferior to PDS	More common with PDS
CHORUS,[9] 2004-2010	Noninferiority, 87 hospitals in UK and New Zealand	No, III-IV, 550	PDS NACT	17 39	41 73	10.7 12	22.6 24.1	NACT noninferior to PDS	More common with PDS
SCORPION,[10] 2011-2016	Superiority, single institution	No, IIIC-IV, 171	PDS NACT	45.5 57.7	92.8 100	15 14	41 NR	NACT not superior to PDS	Early grade 3/4: 52.7% 5.7%
JCOG0602,[11] 2006-2011	Noninferiority, multiple sites in Japan	No, III-IV, 301	PDS NACT	12 64	37 82	15.1 16.4	49 44.3	NACT noninferiority not confirmed	More common with PDS
TRUST,[15] 2016-2019	Superiority, multiple sites in Europe & US	Yes, IIIB-resectable IVB, 686	PDS NACT						

CGR, complete gross resection; mo, months; EORTC, European Organisation for Research and Treatment of Cancer; JGOG, Japanese Gynecologic Oncology Group; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; RD, residual disease.

[a]CGR defined as no residual disease.

[b]Optimal RD defined as one or more tumor nodules 1-10 mm in maximal dimension.

recently reached accrual and is currently closed. Results on the primary outcome (OS) are anticipated in 2024.

Ultimately, the decision to proceed with NACT vs PDS depends on many factors, including patient fitness and the volume and distribution of disease. The current scientific evidence supports either approach in well-selected patients. With both PDS and NACT/IDS, the best outcomes are achieved in patients who have a CGR. Further investigation is needed into the development of intraoperative techniques and postoperative care to facilitate the safe accomplishment of this goal in as many patients as possible.

Surgery for Recurrent Disease

Since 1983, when Berek and colleagues reported on secondary cytoreductive surgery (SCS),[16] the body of literature reporting on this procedure has grown. A Cochrane review published in 2013 evaluated 1194 patients with recurrent ovarian cancer and showed that OS was significantly prolonged when complete resection was achieved at SCS (HR, 3.59; 95% CI, 2.45-5.24).[17] Patient selection remains the most crucial aspect in the appropriate utilization of SCS.

The German Oncology Group (AGO) sought to create a preoperative algorithm to identify surgical candidates for secondary cytoreduction. The researchers undertook the development and validation of a predictive score and published a series of papers known as the DESKTOP OVAR trials. DESKTOP I was a retrospective review of 267 patients with platinum-sensitive (platinum-free interval >6 months) recurrent ovarian cancer that explored the clinical variables associated with achieving a complete resection during SCS. Complete resection was associated with longer OS compared with any residual disease (median OS, 45.2 vs 19.7 months; HR, 3.71; 95% CI, 2.3-6.1). The final AGO score for predicting complete resection is composed of an Eastern Cooperative Oncology Group (ECOG) performance status of 0, ascites volume of less than 500 mL, and CGR at the time of initial surgery. When these factors are combined, a positive AGO score has a positive predictive value (PPV) of 79%.[18] DESKTOP II was designed to validate

Table 2. Memorial Sloan Kettering Criteria for the Selection of Patients for Secondary Cytoreductive Surgery According to Disease-Free Interval and Number of Sites of Recurrence

DFI, mo	Single Site	Multiple Sites Without Carcinomatosis	Carcinomatosis
6-12	Offer SCS	Consider SCS	Do not offer SCS
12-30	Offer SCS	Offer SCS	Consider SCS
>30	Offer SCS	Offer SCS	Offer SCS

DFI, disease-free interval; mo, months; SCS, secondary cytoreductive surgery.

Source: Cowan RA, Eriksson AGZ, Jaber SM, et al. *Gynecol Oncol*. 2017;145(2):230-235.[21]

the AGO score prospectively. Over a 19-month period, 516 patients were screened, of whom 51% (n=261) were classified as having a positive score. A total of 129 patients underwent SCS and 76% of these had a CGR, thus validating the score in this population. DESKTOP II reported a moderate complication rate, including reoperation in 11% of patients, and a perioperative mortality rate of 0.8%.[19] DESKTOP III was an RCT of 407 patients with a positive AGO score who were randomly assigned to SCS or no surgery. PFS was significantly longer in the patients who underwent SCS vs no surgery (18.4 vs 14.0 months; HR, 0.66; 95% CI, 0.54-0.82), and the time to first subsequent therapy also favored the surgery arm (21 vs 13.9 months; HR, 0.61; 95% CI, 0.48-0.77).[20] The results for the primary outcome (OS), presented at the 2020 ASCO annual meeting, significantly favored SCS over no surgery (median OS, 53.7 vs 46.0 months; HR, 0.75; 95% CI, 0.58-0.96; *P*=.02).[20] Although the AGO score has been successfully validated, there is concern that the score is too restrictive and may exclude some patients who could benefit from an attempted SCS.

Other groups have also developed and reported on patient selection algorithms. The Memorial Sloan Kettering (MSK) criteria were created to predict CGR on the basis of disease-free interval (DFI) and distribution of tumor regrowth (Table 2). At 10-year follow-up, the adherence rate with the algorithm for patient selection was 98%, leading to an 86% CGR rate.[21] OS was significantly increased in patients with a CGR at the time of SCS vs those with visible residual disease (95.6 vs 57.5 months; *P*=.014). A recent publication from the Mayo Clinic supports DFI as an important prognostic factor for OS after SCS.[22]

GOG protocol 0213 investigated the role of SCS in platinum-sensitive recurrent ovarian cancer in the setting of an RCT. The trial had 2 components: (1) a nonsurgical objective, to evaluate the role of concurrent and maintenance bevacizumab,[23] and (2) evaluation of the role of SCS in the same cohort.[24] Surgical candidacy was based on provisional guidance that the investigating surgeon anticipated CGR to be achievable. Patients were randomly assigned to SCS or chemotherapy alone. The original design of the surgical arm was a superiority trial, with a target of improving OS by 30% by adding surgery (HR, 0.7). Within the surgical arm, 485 patients were deemed to be surgical candidates, of whom 240 were randomized to SCS; 225 patients ultimately underwent SCS with a CGR rate of 67%. Although PFS was better in the patients with CGR vs no surgery (21.4 vs 16.5 months; HR, 0.68; 95% CI, 0.51-0.9), no statistical difference was noted between OS in the 2 arms, and the curve favored chemotherapy alone (54 months for SCS vs 66 months for chemotherapy alone; HR, 1.28; 95% CI, 0.92-1.78). One potential explanation for this unexpected result is the fact that more than 80% of the patients who underwent SCS had been exposed to bevacizumab, which may have interfered with the effect of surgery.[25] Trial participants were not stratified for *BRCA* mutations, which have been shown to occur in up to 25% of patients with EOC[26] and to have a favorable effect.[27] Further analyses are under way to determine if *BRCA* or homologous recombination deficiency (HRD) status influenced the results, as these were not accounted for in the original analysis.[28,29]

A large retrospective series investigating the effect of SCS in a cohort of 626 patients with recurrent platinum-sensitive ovarian cancer was published by Gockley and colleagues. This cohort study, with data collected from 2004 to 2011, compared SCS (23%, n=146) with chemotherapy alone (77%, n=480). Using propensity score matching, they found the median OS to be 54 months with SCS vs 33 months with chemotherapy alone (*P*<.001).[30] The OS for SCS is comparable to that reported in GOG-0213, which recruited patients during a similar time frame (2007-2011).

Although the data suggest that SCS is safe and feasible for selected patients with recurrent platinum-sensitive EOC, the mixed data raise questions regarding its efficacy and the optimal selection criteria. Comparing across trials, it is worth noting that SCS was associated with improvement in PFS in both GOG-0213 and DESKTOP III, and improvement in OS and interval to first treatment in DESKTOP III. Prolonged DFI and prolonged time

off treatment may be associated with improved quality of life (QOL) among patients with recurrent disease; patient-centered outcomes are valuable endpoints for inclusion in future trial designs.[25]

Optimizing Surgical Outcomes

Pushing the Limits to Achieve a Complete Gross Resection

In 1975, the inverse relationship between residual tumor burden and OS was described in a landmark paper by Griffiths.[31] Since then, growing evidence has indicated that the volume of residual disease following debulking surgery strongly correlates with OS.[3-7,32,33] The greatest survival benefit is seen when CGR is achieved.[7,25] To achieve CGR, complex cytoreductive surgery is often necessary and includes resection of disease in the upper abdomen. The repertoire of procedures includes, but is not limited to, the following: diaphragm stripping, splenectomy, dissection of the porta hepatis, liver resection, and distal pancreatectomy.[34,35] Tseng and colleagues published a single institution's experience spanning a 13-year period in which paradigm shifts in surgical practice to include extensive upper abdominal surgery, and changes in the goal of surgery from minimal residual disease to no gross residual disease, were analyzed for their effect on OS.[36] The results of this retrospective review demonstrated increasing rates of CGR (from 29% to 55%) and optimal resection (from 77% to 86%) over time. Rates of 5-year PFS (from 15% to 20%) and OS (from 40% to 56%) also improved during the study period. Although this study focused on surgical outcome at the time of PDS, these techniques have also facilitated improved CGR rates in the setting of interval debulking and surgery for recurrent disease.

Who Is a Surgical Candidate for Primary Debulking Surgery?

Aggressive cytoreductive surgery is not without risk for morbidity and mortality, and a careful selection of patients for fitness is required. Older age, poor performance status, larger volume and extent of disease, and poor preoperative nutritional status are predictors of worse postoperative morbidity.[37] Tailored approaches to primary management have been developed. A commonly used algorithm is based on the criteria described by Aletti and colleagues, whereby patients with all 3 of the following parameters, associated with high rates of perioperative morbidity, are triaged to NACT: (1) age older than 75 years, (2) serum albumin level below 3.5 g/dL, and (3) American Society of Anesthesiologists classification score of 3 or higher or extensive disease.[38] This strategy allows mindful selection of the subset of patients likely to benefit from NACT, while maximizing the cohort proceeding to PDS.

Laparoscopic Scoring Systems to Aid Triage in Primary Management

Laparoscopic scoring systems have been developed to help triage patients to PDS or NACT according to the presence or absence of disease in specified locations. Most notable is the Fagotti scoring system, which assigns either 0 or 2 points according to the absence or presence of disease, respectively, in 7 anatomic locations: omental caking, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, bowel and/or stomach infiltration, spleen metastasis, or liver superficial metastasis. A score of at least 8 has a PPV of 100% and a negative predictive value (NPV) of 70% for suboptimal debulking.[39,40] In a quality improvement project conducted at a single large institution, a broad application of diagnostic laparoscopy with use of the Fagotti score led to improved rates of CGR (88%) in patients who underwent PDS.[41] Because advances in surgical technique and increases in the degree of aggressiveness have occurred,[42,43] the authors of that study proposed increasing the score threshold to 10. This notion is further supported by a study of 234 patients with newly diagnosed EOC who underwent laparoscopic assessment; CGR rates were 57.5%. When a higher score was used, the PPV for the presence of residual disease was 100%.[44] A recently published prospective randomized trial comparing PDS vs diagnostic laparoscopy followed by triage to PDS or NACT showed that the rate of futile laparotomy (defined as >1 cm of residual disease—ie, suboptimal debulking) was lower in the laparoscopy group (10% vs 39%; relative risk, 0.25; 95% CI, 0.13-0.47).[45] The use of diagnostic laparoscopy may maximize tumor removal while decreasing the rates of futile laparotomy; further investigation into the added costs, operative time, and surgical risk should be incorporated into future study.

Radiologic Resectability Scores

Radiologic resectability scores have been investigated as a noninvasive and low-risk tool to help triage patients to appropriate primary therapy. Suidan and colleagues created a radiologic assessment tool that evaluates patients for the presence or absence of disease in 11 anatomic locations. A score is generated according to the findings and used to predict surgical outcome. The tool was used to create 2 models in the same cohort of patients; the first model predicted the likelihood of a suboptimal resection,[46] and the second predicted the likelihood of a CGR.[47] Kumar and colleagues sought to validate these models with their own ovarian cancer database and independently validated the model predicting CGR.[48] Future directions in the area of preoperative tools applicable to surgical cytoreduction include the development of artificial intelligence to aid in reading preoperative images and predicting surgical outcomes.

What Is the Role of Lymphadenectomy?

Historically, surgical practice varied with regard to lymphadenectomy at the time of debulking surgery, ranging from the removal of only clinically abnormal lymph nodes to complete systematic lymphadenectomy for all patients. The LION trial sought to evaluate the role of lymphadenectomy at the time of PDS in women who had normal nodes preoperatively and intraoperatively.[49] This prospective RCT evaluated 647 women who underwent complete cytoreductive surgery and systematic pelvic and paraaortic lymph node dissection (LND) vs no LND. No differences were found between PFS (HR, 1.11; 95% CI, 0.92-1.34) or OS (HR, 1.06; 95% CI, 0.83-1.34) in the 2 groups. More operative and postoperative complications developed in the women who underwent LND, including a longer operative time, greater blood loss, greater transfusion requirement, and more intensive care unit admissions. Interestingly, of the patients who underwent LND, 55.7% had positive lymph nodes on final pathologic inspection. In patients who have a CGR and normal-appearing lymph nodes, LND adds no benefit and entails more morbidity.

Surgical Approach

Laparoscopy vs Laparotomy at the Time of Interval Debulking Surgery

CGR is an independent prognostic factor for OS following debulking surgery and should be the goal of surgery, with few exceptions.[3,35,36,50,51] In the majority of patients, achieving this goal entails a major operation with the potential for significant morbidity. In the RCTs evaluating PDS vs NACT, the patients who underwent NACT followed by IDS had less morbidity.[8,9,12] Interest has been growing in the potential role of minimally invasive surgery (MIS) in the setting of IDS and its potential effect on morbidity and the ability to achieve CGR. In 2016, Aletti and colleagues published a phase 2 multicenter study (MISSION) evaluating minimally invasive debulking surgery in patients with stage III-IV advanced EOC who had a complete response following NACT according to Response Evaluation Criteria in Solid Tumors (RECIST).[52,53] During the study period, 28% (52/184) of the patients with advanced EOC who had received NACT met the inclusion criteria, and 30 of the patients (16%) underwent the planned MIS. The CGR rate was 96.6%, with an optimal resection rate of 100%. This study showed that MIS was safe and feasible in highly selected patients; however, long-term survival data were not available.

A recently published retrospective cohort study used the National Cancer Database to identify 3071 patients with stage IIIC-IV ovarian cancer treated with NACT and IDS between 2010 and 2012. They found no difference in 3-year survival between patients treated with MIS vs laparotomy (47.5 vs 52.6 months; *P*=.12).[54] It is important to note that the patients in the study who underwent MIS were more likely to undergo excision of only gynecologic structures, without additional cytoreductive procedures, than were the patients who underwent laparotomy, and therefore they may represent a group with a lesser disease burden. The trend that patients undergoing MIS will have less extensive procedures is further supported by another retrospective review comparing MIS vs laparotomy, in which no patients undergoing MIS had a hepatic resection or a gastrointestinal resection.[55]

Patient selection is key to the application of MIS in the surgical management of advanced EOC; the goal of surgery must remain CGR regardless of the approach. Retrospective data from a single institution presented at the 2019 Society of Gynecologic Oncology annual meeting showed that women undergoing IDS require bowel surgery 32% of the time and surgery in the upper abdomen 51% of the time.[56] At IDS, patients may require extensive procedures that can be difficult to complete laparoscopically. To date, no level 1 evidence exists comparing MIS with traditional laparotomy in the setting of debulking surgery for EOC. RCTs with stringent surgical quality control are needed to help define patient selection, evaluate surgical outcomes, and investigate the long-term prognostic effects on OS.

Novel Concepts in Surgery

What Is the Role of Hyperthermic Intraperitoneal Chemotherapy?

A phase 3 multicenter randomized controlled trial published in 2018 by van Driel and colleagues evaluated the use of hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of IDS vs IDS alone.[57] Patients included in this study had newly diagnosed stage III EOC, had received NACT owing to extensive abdominal disease, and were not eligible for PDS. Patients were randomized in a 1:1 ratio at the time of surgery if CGR or optimal resection was anticipated. The primary endpoint was recurrence-free survival (RFS). RFS was improved in the patients in the HIPEC arm, with a median HR of 0.66 (95% CI, 0.50-0.87; *P*=.003). A secondary endpoint was OS, which was improved in the patients in the HIPEC arm (HR, 0.67; 95% CI, 0.48-0.94; *P*=.02) compared with those in the standard arm. Importantly, no difference was found between the rates of serious postoperative adverse events in the 2 arms (*P*=.76). HIPEC at the time of IDS is now listed as an option in the National Comprehensive Cancer Network (NCCN) guidelines for the primary management of EOC as a level 2A recommendation.[58] Currently, the use of HIPEC at the time of PDS

is not supported by the literature; however, a multicenter international RCT investigating this question is planned.

What Is the Role of HIPEC at the Time of Secondary Cytoreduction?

Interest continues in the role of HIPEC at the time of SCS for the treatment of recurrent EOC. Among a large retrospective series of 249 patients who had persistent or recurrent EOC treated with debulking surgery and HIPEC, optimal resection was achieved in 92.2%. Excellent outcomes were reported in the sub-cohort of 184 patients with platinum-sensitive disease, with a median OS of 52 months.[59] Despite these promising results, a recent phase 2 RCT presented by Zivanovic and colleagues at the 2020 ASCO annual meeting showed no significant difference between PFS or OS in patients with platinum-sensitive recurrent disease who underwent SCS with or without HIPEC (agent: carboplatin at 800 mg/m^2).[60] A phase 3 randomized clinical trial is currently under way to evaluate HIPEC in the recurrent setting (CHIPOR; NCT01376752). The trial is evaluating patients with platinum-sensitive relapsed ovarian cancer undergoing cytoreductive surgery with CGR alone vs cytoreductive surgery with CGR and HIPEC (agent: hyperthermic cisplatin at 75 mg/m^2). OS is the primary outcome; RFS is a secondary outcome. The estimated enrollment is 444 participants, with completion anticipated in 2025. This study is temporarily suspended because of the COVID-19 pandemic.[61]

Surgical Quality Control in Studies

In surgical trials, the value of surgical quality control with standardized metrics is increasingly recognized as a priority, and awareness is growing regarding the necessity of incorporating this in trial design. Several practice-changing clinical trials published over the last decade have been criticized for lacking appropriate surgical quality control. The EORTC study of Vergote and colleagues had a median operative time of 2 hours in both arms, with CGR rates of merely 20% in the PDS arm and 50% in the NACT/IDS arm.[8] These numbers are in stark contrast to those of retrospective data published during the same time,[36] calling into question whether the data are generalizable to high-volume surgeons and centers.[25]

Pharmaceutical trials of therapeutics employ rigorous protocols to ensure uniform application of the experimental agent. Designing such protocols is a greater challenge in a surgical study, but rigorous surgical quality control is gaining acceptance. All participating centers in the LION trial were evaluated for proficiency in lymphadenectomy before patient enrollment.[49] Similarly, the TRUST trial employed a very rigorous surgical quality control program, including but not limited to in-person site visits with surgical observations and chart review. All enrolling sites in the TRUST trial had to document a CGR rate higher than 50% and the performance of at least 36 debulking surgeries per year.[15] Employing quality measures to ensure surgical rigor as a foundation of study design will help minimize biases in the outcomes and allow broader application of the results.

Patient Preferences and Patient-Reported Outcomes

Patient Preferences

As management options for patients with advanced EOC become more complex, their preferences regarding the trade-offs between survival benefits and QOL must be incorporated into trial outcomes and individualized treatment planning. It has been shown that centralized care at specialized cancer centers improves survival in patients who have ovarian cancer, with better adherence to NCCN guidelines and increased rates of optimal resection.[62] A recent cross-sectional study evaluating the willingness of patients to travel for more centralized care showed that 81% (50/62) were willing to travel an additional 50 miles for surgical treatment if doing so led to a 6% increase in 5-year survival. However, 1 in 5 patients preferred not to travel 50 miles despite being counseled regarding the survival benefit.[63]

Seeking to better understand and quantify the preferences of patients with ovarian cancer regarding primary management, Havrilesky and colleagues used a survey to evaluate the trade-offs between the risk for adverse events and survival outcomes. This was the first study to quantify patients' preferences for PDS vs NACT in a formal manner. Among the 101 women with ovarian cancer enrolled in the study, OS (36/100) was weighted as the most important concern, followed by complications requiring readmission (23/100), PFS (19/100), surgical mortality (16/100), extent of surgery (4/100), and treatment order (PDS vs NACT; 2/100). Patients were willing to accept an increase in risk for mortality of 4 percentage points (95% CI, 2%-13%) in return for an increase of 6 months in OS (from 3.0 to 3.5 years).[64] The decision-making process regarding the primary management of ovarian cancer is challenging for both patient and provider. These studies offer quantified data to help frame the discussion.[65] Furthermore, understanding patient preferences can inform the design of future trials.

Patient-Reported Outcomes

Little is known about patient-reported outcomes in the ovarian cancer population. Whereas postoperative morbidity and mortality are quantifiable, knowledge about the patient experience during the postoperative recovery period

is lacking. Using a validated tool, Meyer and colleagues recently compared patient-reported symptom burdens in patients who underwent PDS vs IDS. They found that the timing of surgery did not affect the severity of symptoms immediately following surgery or in the extended period following postoperative discharge. Patients who underwent procedures that had higher surgical complexity scores were more likely to have fatigue, pain, nausea, and higher total scores while in the hospital irrespective of the timing of surgery.[66] Further investigations into patients' experiences regarding trade-off between the risks and benefits, such as increased time off treatment and OS, of treatments will provide invaluable information.

Conclusion

The landscape of the management of advanced ovarian cancer is continually changing. Surgical debulking remains an integral aspect of high-quality care. As our understanding of the heterogeneity of this disease grows, a personalized approach to the surgical management of patients in both the primary and recurrent settings is warranted. Residual disease following debulking surgery remains the most important modifiable factor affecting survival, and new inquiries should focus on maximizing the availability of safe and high-quality surgical debulking for the majority of patients.

Disclosures

No conflicts of interest are reported. Dr Straubhar reports a patent (W02019195097A1) for a perineal heating device outside the submitted work. Dr Chi reports personal fees from Bovie Medical, Verthermia Acquisitions (now Apyx Medical Corporation), CSurgeries, and Biom'up, and previously owned stocks from Intuitive and TransEnterix outside the submitted work. Dr Roche reports travel expenses from Intuitive outside the submitted work.

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