

The Current Status of Secondary Cytoreduction in Ovarian Cancer: A Systematic Review

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Abstract: *Purpose:* Ovarian cancer causes more deaths than any other cancer of the female genital tract. Despite improvements in management and treatment, survival remains low in patients with extensive disease at presentation, which usually leads to eventual recurrence. Treatment of recurrence remains challenging. Although the use of secondary cytoreduction to treat recurrent disease has become widespread, its utility remains unproven. *Methods:* This systematic review examines all the relevant electronic literature. An electronic literature search was conducted in the PubMed, MEDLINE, and EMBASE databases from January 1980 through December 2019. *Results:* Several relevant retrospective studies have been published, and these unanimously suggest that secondary cytoreduction is associated with an increase in progression-free and overall survival after relapse. Despite sound statistical methods, these studies are unfortunately limited by significant confounding inherent to the retrospective approach and by selection bias, given that healthier patients with less disease have historically been selected for surgery. Data from clinical trials are currently evolving. Early data from DESKTOP III demonstrate improved progression-free survival with secondary cytoreduction, whereas GOG-0213 found no difference in progression-free or overall survival. *Conclusions:* Secondary cytoreduction remains a viable treatment option for select patients for now, but this is entirely dependent on the highly anticipated overall survival results of DESKTOP III and SOC 1.

Introduction

Ovarian cancer causes more deaths than any other cancer of the female genital tract, with more than 21,750 new cases and 13,940 deaths anticipated in the United States in 2020.¹ Despite substantial efforts to develop screening protocols and improve treatment modalities, ovarian cancer continues to be a vexing malignancy with high mortality. Poor long-term survivorship is a function of both widespread disease at presentation and the eventual development of resistance to chemotherapeutic agents, which leads to a recurrence in 70% to 90% of patients.^{2,3} Recurrent ovarian cancer remains a

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Gynecologic oncology, ovarian cancer, recurrent ovarian cancer, secondary cytoreduction

considerable clinical challenge, with limited treatment options. Although primary and interval cytoreductive surgeries have well-established, essential roles in treatment, the efficacy of secondary cytoreductive surgery for recurrent ovarian cancer remains controversial.

Secondary cytoreduction (SC) for recurrent ovarian cancer is defined as surgery to debulk a tumor that recurred after the patient completed a primary treatment regimen that led to a period of remission. It was first described in the literature in the early 1980s. By 1996, the National Comprehensive Cancer Network was recommending SC as a treatment option in ovarian cancer.^{4,5} As in the primary setting, surgery at the time of recurrence provides a theoretical benefit by reducing the overall tumor burden and removing disease with a poor blood supply in order to increase the efficacy of subsequent chemotherapy.⁶

Although the procedure is beneficial in theory, published studies have found mixed results. According to a Cochrane review from 2013, for women with platinum-sensitive recurrent ovarian cancer, complete cytoreduction is associated with improved overall survival (OS) compared with incomplete resection.⁴ However, no comparisons were made with patients receiving chemotherapy alone. This effect may therefore be related to selection bias, given that patients with more favorable tumor biology tend to have a more complete cytoreduction.⁷ An additional Cochrane review from 2010 aimed to compare the efficacy and safety of cytoreduction plus chemotherapy vs chemotherapy alone, but was unable to identify any relevant studies that met their selection criteria.⁸ Additionally, the clinical value of SC appears equivocal in light of the recently presented results from 2 randomized phase 3 trials, GOG-0213 (Carboplatin, Paclitaxel and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian, Epithelial, Primary Peritoneal, or Fallopian Tube Cancer) and DESKTOP III (Study Comparing Tumor Debulking Surgery Versus Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer).^{9,10} Herein, we review the evidence for factors that can predict complete resection with SC, thus allowing for optimal patient selection. Furthermore, we critically assess the efficacy and the role of SC in the contemporary treatment of ovarian cancer.

Methodology

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, with the objective of evaluating the effect of secondary cytoreductive surgery on survival. PubMed, MEDLINE, and EMBASE were used to identify contributing research to the topic from

January 1980 through December 2019. Furthermore, article reference lists were reviewed for inclusion of additional references. Key words included “ovarian cancer,” “secondary cytoreductive surgery,” “recurrence,” and combinations of these terms. Studies selected included randomized controlled trials (RCTs) as well as prospective and retrospective studies that directly compared treatment with SC and chemotherapy vs chemotherapy alone for recurrent ovarian cancer. The analysis excluded studies such as case reports, case series, reviews, expert opinions, feasibility studies, and studies without an appropriate control to allow for a direct comparison. Additionally, studies combining hyperthermic intraperitoneal chemotherapy with SC were not within the scope of this review.

In total, 876 records were identified (Figure). References were managed using Rayyan QCRI.¹¹ After merging references from each database into a single set, 304 duplicate references were identified and removed. A total of 179 references were excluded for subject matter unrelated to SC. Many of these references focused on any surgery for ovarian cancer, primary cytoreduction, second-look surgery, interval cytoreduction, or higher-order cytoreductive surgery. A total of 114 references were excluded for being a review, an expert opinion, or a summary of a conference debate. A total of 109 were excluded for having an outcome, population, or study design that did not yield comparison of either OS or progression-free survival (PFS). Ninety studies were classified as either case reports or feasibility studies for very specific surgeries or procedures. Full text in English was unavailable for 5 studies. After applying exclusion criteria, an additional 55 studies were excluded owing to lack of an appropriate control for comparison between groups. A total of 18 studies were identified for review, including 16 retrospective studies and 2 RCTs.

Results

Who Appears to Benefit From SC?

SC has received a great deal of attention since 1983, when a retrospective analysis by Berek and colleagues found median survival to be 20 months in patients with optimal cytoreduction (defined as <1.5 cm) vs 5 months in patients with suboptimal debulking.⁵ In 2001, Scarbali attempted to identify prognostic factors for survival in recurrent ovarian cancer by performing a prospective study with 149 consecutive patients who met selection criteria for SC. Complete SC was by far the most predictive factor in this study (hazard ratio [HR], 2.65; 95% CI, 1.43-4.92).¹² Several studies demonstrate that survival is improved with chemotherapy plus SC vs chemotherapy alone. For example, Bickell and colleagues performed an analysis of 2038 patients with recurrence

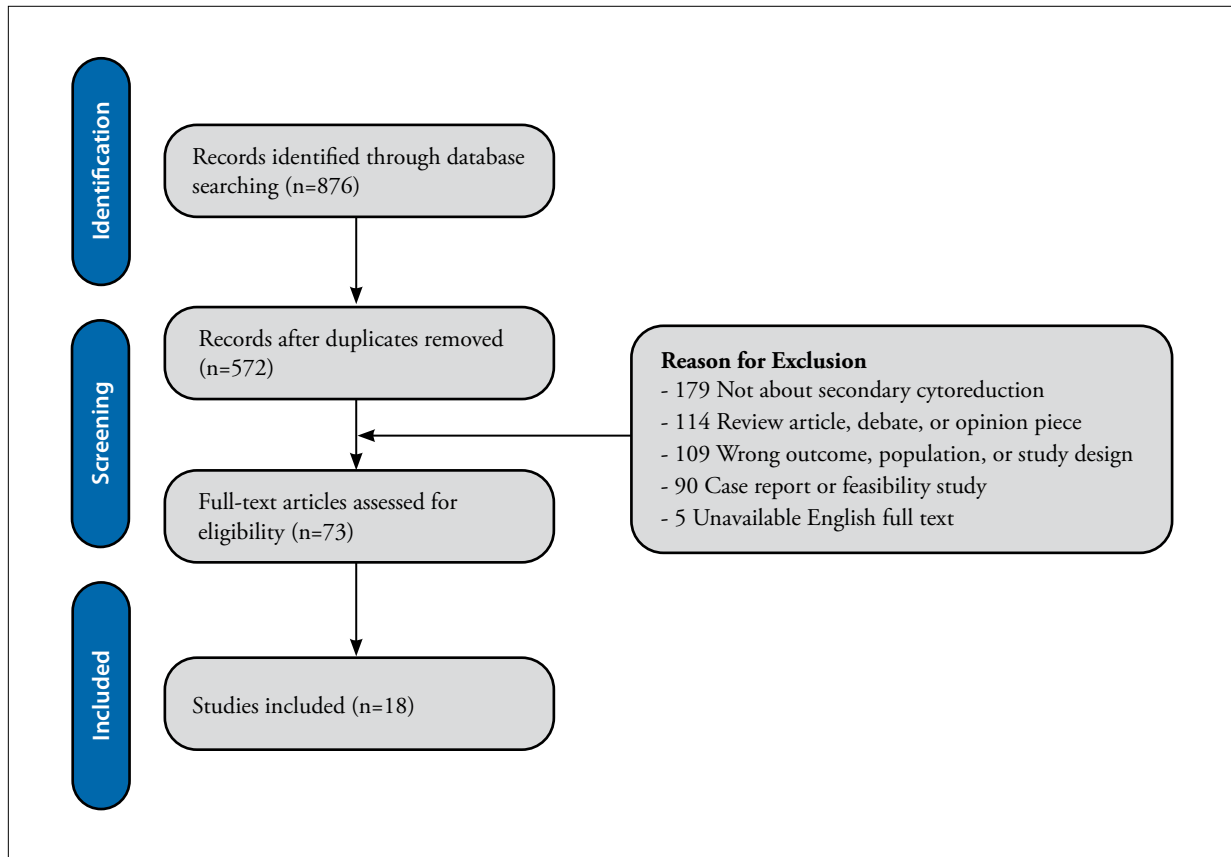


Figure. PRISMA diagram.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

in the Surveillance, Epidemiology, and End Results (SEER) database who were propensity-score matched for demographic variables, stage, grade, histology, and comorbidities. Median survival was 5.4 years among the 16% who were treated with surgery and chemotherapy vs 4.1 years among the 72% of patients who received chemotherapy alone (HR, 1.67; 95% CI, 1.13-2.47).⁷ Multiple meta-analyses have demonstrated that complete surgical debulking to no gross residual disease, or complete gross resection (CGR) leaving no residual cancer that is observable (CGR-R0), is associated with increased OS.^{4,13}

Since that time, numerous studies have reinforced the finding that survival is improved with SC, and in particular with complete or optimal SC. Although initially designed to select patients who might benefit from SC, the 2006 DESKTOP I trial (Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer) by Harter and colleagues suggested that SC in platinum-sensitive recurrent ovarian cancer could improve median OS from 19.7 to 45.2 months

when resection was complete.¹⁴ Oksefjell and colleagues demonstrated that after SC, median OS was 4.5 years for patients with no residual tumor, 2.3 years for those with tumors of 2 cm or less, and 0.7 years for those with tumors greater than 2 cm. In contrast, median OS was only 13.2 months for those receiving chemotherapy alone.¹⁵ Tian and colleagues had similar results in favor of complete SC, with a median survival of 63.2 months for patients with R0 resections, 31.1 months for those with R1 resections (the removal of all macroscopic disease), and 15.6 months for those with R2 resections (gross residual disease; $P < .01$).¹⁶ Sehouli and colleagues reported an OS of 42.3 months with R0 resections, 17.7 months with R1 resections, and 7.7 months with R2 resections ($P < .001$).¹⁷

Patient Selection: Can We Predict Who Will Have a Complete Resection at SC?

SC appears to benefit well-selected patients when CGR-R0 is achieved. Therefore, much effort has focused on how to identify patients in whom SC is likely to lead to complete resection. Early studies, such as one by Zang

and colleagues from 2004, showed strong associations between the extent of disease relapse and the success of SC. That is, optimal SC was achieved in 87.9% of patients with a solitary site of recurrence vs 51.2% of those with multiple sites of recurrence, resulting in a substantial difference in survival (relative risk [RR], 9.1237; $P=.0002$).¹⁸ Likewise, in 2006, Chi and colleagues at Memorial Sloan Kettering (MSK) sought to identify prognostic factors that predicted survival. They found that the disease-free interval ($P=.004$), the number of sites of recurrence ($P=.01$), and residual disease after SC ($P<.001$) were significant prognostic factors.¹⁹ Based on these data, the authors proposed selection criteria (MSK criteria) for successful SC: patients with a single site of recurrence, those with multiple sites without carcinomatosis and a disease-free interval of at least 12 months, and those with carcinomatosis and a disease-free interval of at least 30 months. Associations such as these prompted the development of several scoring systems to further guide patient selection for SC.

AGO Score. The DESKTOP I study from the German Gynecological Oncology Group (AGO) was performed with the goal of creating a panel of criteria to select patients who may benefit from secondary cytoreductive surgery.¹⁴ This multicenter retrospective study noted that complete resection was associated with significantly prolonged survival (45.2 vs 19.7 months; $P<.001$) and identified 4 key variables that were associated with complete resection: Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, International Federation of Gynecology and Obstetrics (FIGO) stage at diagnosis (I/II vs III/IV; $P=.036$), residual tumor after primary surgery (none vs present; $P<.001$), and less than 500 mL of ascites at recurrence ($P<.001$). In multivariate analysis, stage was excluded, and patients who satisfied the remaining 3 criteria had complete resection in 79% of cases, although 42% of patients with a negative score also achieved a complete resection.

DESKTOP II was performed with the goal of prospectively validating the results from DESKTOP I, with the incorporation of these criteria. It found that the AGO score could predict 76% of patients who would benefit from SC.¹⁹ It should be noted, however, that this study was not randomized and did not report results for score-negative patients.²⁰ Two retrospective studies also attempted to validate the AGO scoring. Muallem and colleagues performed a retrospective analysis on 209 consecutive patients who underwent SC.²¹ Of those with an AGO-positive score, 67% achieved total macroscopic cytoreduction. Of the AGO-negative patients, 49% also achieved optimal cytoreduction. No significant differences in morbidity or mortality were observed based on

the AGO score when optimal resection was achieved. Janco and colleagues noted similar results, with 84.3% of AGO-positive patients and 64.4% of AGO-negative patients achieving optimal cytoreduction.²²

Tian Score. Tian and colleagues conducted an international retrospective review of patients from 9 different cohorts spanning from 1982 to 2006, including the AGO cohort.²³ This study found that complete SC correlated with FIGO stage, residual disease after primary cytoreduction, progression-free interval, ECOG performance status, CA-125, and ascites at recurrence. The authors created a scoring system based on these variables to stratify patients as high- or low-risk for nonoptimal cytoreduction. Complete cytoreduction was achieved among 53% of the low-risk patients vs only 20.1% of the high-risk patients. The researchers additionally performed a small external validation that demonstrated a sensitivity of 83% and a specificity of 57.6%

Comparison of Scoring Systems. In an analysis from 2015, van de Laar and colleagues found that the positive predictive value of complete gross resection was 82.0% with the AGO score and 80.3% with the Tian score.²⁴ Unfortunately, the false negative rate was 68.5% and 55.6%, respectively. The Tian score was associated with improved overall survival, but the AGO score was not. Cowan and colleagues examined compliance and outcomes of the MSK selection criteria in predicting CGR-R0, and they directly compared these criteria with the AGO and Tian scores in the same patient population.²⁵ The authors found that the rate of complete gross resection was 86% after implementation of the MSK criteria. The AGO model was found to be stricter, with 51% of cases being excluded. The Tian model proved to have a high degree of concordance with the MSK criteria. Notably, when applied to their intermediate “consider SC” group, the MSK criteria successfully predicted the outcome in 26 of 29 patients, suggesting the potential for a combinatorial scoring system. It is important to note that the population in this study was skewed; all but 5 patients met the MSK criteria.

Although each of these scoring systems would appear to have relative strengths and weaknesses in predicting CGR-R0, the AGO score remains the only prospectively validated set of selection criteria. Additionally, the AGO score currently has level 1 evidence supporting its use, in the form of increased PFS in DESKTOP III.⁹

Combined FDG-PET and Laparoscopic Evaluation. A combination of fluorodeoxyglucose positron emission tomography (FDG-PET) and laparoscopy has also been used to predict whether patients will achieve CGR-R0

with SC. The accuracy of this method has been reported as 81%, vs 54% for the AGO score.²⁶ Nearly 20% of patients with a negative AGO score achieved successful SC after evaluation by PET/computed tomography and laparoscopy, suggesting that despite the negative AGO score, they were good candidates for SC.²⁷ The AGO score was found to be very reliable among patients who underwent SC after FDG-PET and laparoscopic evaluation, with a positive predictive value of 91.7% and a negative predictive value of 86.7%.²⁷ However, 48 of 150 AGO score–positive patients (32%) were judged unresectable by laparoscopy. Although these results are promising, the data are retrospective, and the approach adds an additional surgery to treatment of patients who are found to not be candidates for SC via laparoscopy. In addition, this procedure can be associated with potential complications, and the time required for healing afterward would delay administration of chemotherapy, possibly mitigating any benefits.

Toxicity and Adverse Events Associated With SC

Even if the addition of SC to the treatment regimen improves survival, surgery is not without inherent risks of complications and morbidity. Early studies reported morbidity rates ranging from 7.7% to 63%, with variations related to differences in patient selection, surgical aggressiveness, and definitions of morbidity.^{5,18,28,29} Woelber and colleagues found similar complication rates between primary and secondary cytoreduction, although perioperative morbidity was reported in 44% of patients receiving SC vs 36% of those undergoing primary surgery.³⁰ In studies focusing on minimally invasive SC, complication rates have been lower: Gallotta and colleagues found a 6.8% rate of intraoperative complications and a 10.3% rate of postoperative complications.³¹ Of note, all patients in this study achieved complete debulking, and most just had isolated nodules, indicating that selection criteria may have influenced these complication rates. Eriksson and colleagues reported similar results, with an 8% postoperative complication rate for minimally invasive SC relative to 22% for SC conducted via laparotomy.³² Gockley and colleagues, in a propensity score–matched cohort, found that taken together, several complications—including anemia, infection, thromboembolic events, cardiac or cerebrovascular events, pneumonia or respiratory failure, rehospitalization, and intensive care unit admission—were more frequent for patients undergoing surgery, although no individual complication achieved statistical significance.³³ However, this study was likely underpowered to detect differences in individual complications. In evaluating randomized data, GOG-0213 reported a 30-day surgical morbidity rate of 9%, and a rate of morbidity from surgical complications

of 0.4%. Although quality of life was decreased in the immediate postoperative period, no difference was seen after recovery at 6 weeks and thereafter.¹⁰ Although complication rates are reported for SC procedures, further morbidity data associated with diagnostic laparoscopy or laparotomy performed specifically to assess suitability of SC are needed.

Should We Perform SC? Efficacy Data From Retrospective SC Studies

Since 2003, several retrospective studies have been performed that directly compared SC with chemotherapy vs chemotherapy alone. The results of these studies unanimously supported the finding that survival was improved by the addition of SC to the treatment regimen (Table 1).

Although some of the studies have attempted to compare similar groups of patients, these studies are weakened by a lack of randomization, leading to selection bias. The patients undergoing surgery had more limited disease with fewer sites of recurrence,³⁴⁻³⁶ less ascites,^{34,37} smaller recurrence diameter,^{34,35,38} earlier stage at diagnosis,³⁸ more-localized recurrences,^{15,35-38} fewer symptoms,³⁵ lower CA-125 levels,^{35,36,38} better-differentiated tumors,¹⁵ longer disease-free/platinum-free intervals,^{15,36-39} or less-extensive nodal recurrence.³⁹ Patients receiving surgery also were generally younger,^{15,38,39} with a more-favorable performance status^{15,37,40} and fewer comorbidities.³⁹ In addition to the above-mentioned differences between treatment groups, each of the studies in Table 1 incompletely describes the patient characteristics of the treatment groups, with nearly all missing 1 or 2 essential prognostic factors. This incompleteness often stems from missing data or vague descriptions of selection criteria determined by individual surgeons or at the surgeon's discretion. For example, Lee and colleagues in 2015 performed a secondary analysis on patients from CALYPSO (Caelyx in Platinum Sensitive Ovarian Patients), a large international phase 3 randomized clinical trial comparing carboplatin plus pegylated liposomal doxorubicin vs carboplatin plus paclitaxel.^{38,41} After controlling for several variables in a multivariate analysis, SC was still associated with improved outcomes; however, surgery was performed at the surgeon's discretion, and information about the date of SC and the extent of preoperative disease—such as tumor size and number of metastases—was not available for analysis.

Some of the more modern studies have implemented statistical methods designed to mitigate selection bias. Either classical approaches or variants of multivariate analysis,^{38,42,43} propensity-score matching,^{7,33,44-46} or case control⁴⁷ are the primary methods being used. Although these methods have the power to control for potential confounding variables, every study is missing one or more important prognostic factors in the methods. Moreover,

Table 1. Nonrandomized Retrospective Studies of Secondary Cytoreduction Plus Chemotherapy vs Chemotherapy Alone

Study	Study Type	Groups	N	Optimal Resection, %	Median OS, mo	Median PFS, mo	HR (95% CI) or Log-Rank P Value
Gungor, 2005 ³⁴	Retrospective cohort	SC + chemo vs chemo only	44	77 (R0/R1)	16	NR	OS: <i>P</i> =.03
			31		12		
Matsumoto, 2006 ³⁵	Retrospective cohort	SC + chemo vs chemo only	23	30 (R0)	41.7	NR	OS: <i>P</i> <.01
			23		18.8		
Oksefjell, 2009 ¹⁵	Retrospective cohort	SC + chemo vs chemo only	217	35 (R0)	18.0	NR	NR
			572		13.2		
Gadducci, 2010 ³⁹	Retrospective cohort	SC + chemo vs chemo only	22	NR	Not reached	NR	OS: <i>P</i> =.0002
			44		20.8		
Classe, 2011 ⁴⁰	Retrospective cohort	SC + chemo vs chemo only	35	60 (R0/R1)	35 (optimal)	NR	OS: 0.49 (0.31-0.78)
			73		13 (chemo/R2)		
Chuang, 2012 ⁴⁴	Retrospective cohort	SC + chemo vs chemo only	371	NR	NR	NR	OS: 0.76 (0.66-0.87)
			371				
Gadducci, 2013 ³⁷	Retrospective cohort	SC + chemo vs chemo only	29	85 (R0)	NR	NR	OS: 0.51 (0.28-0.92)
			46				
Lee, 2015 ³⁸	Retrospective cohort	SC + chemo vs chemo only	187	75 (R0)	49.9	18.2	OS: 0.68 (0.52-0.88) DFS: 0.42 (0.33-0.52)
			777		29.7	10.2	
da Costa, 2016 ⁴²	Retrospective cohort	SC + chemo vs chemo only	72	70.6 (R0)	109.5	20	OS: 0.37 (0.19-0.70) PFS: 0.54 (0.36-0.81)
			137		16.3	9.8	
Takahashi, 2017 ⁴⁵	Retrospective cohort	SC + chemo vs chemo only	29 ^a	100 (R0/R1)	58.0 ^b	NR	OS: <i>P</i> =.23 ^a PFS: <i>P</i> =.02 ^a
			29 ^a		24.0 ^b		
Felsing, 2018 ³⁶	Retrospective cohort	SC + chemo vs chemo only	30	93 (<0.25 cm)	54.0	49.8	OS: <i>P</i> =.007 DFS: <i>P</i> =.01
			32		26.2	16.6	
Bickell, 2018 ⁷	Retrospective cohort	SC + chemo vs chemo only	265	NR	64.8	NR	OS: 0.75 (0.68-0.83)
			1171		49.2		

(Table continues on next page)

Table 1. (Continued) Nonrandomized Retrospective Studies of SC Plus Chemotherapy vs Chemotherapy Alone

Study	Study Type	Groups	N	Optimal Resection, %	Median OS, mo	Median PFS, mo	HR (95% CI) or Log-Rank P Value
Gockley, 2019 ³³	Retrospective cohort	SC + chemo vs chemo only	146	70 (R0/R1)	54	NR	OS: 0.45 (0.32-0.65)
			480		33		
Canaz, 2019 ⁴³	Retrospective cohort	SC + chemo vs chemo only	21	38.1 (R0)	NR	NR	PFS: 12.64 (2.69-59.38)
			21				
So, 2019 ⁴⁶	Retrospective cohort	SC + chemo vs chemo only	22	73 (R0)	91.4	21.7	OS: 0.28 (0.11-0.78) PFS: 0.45 (0.22-0.91)
			22		33.4	15.1	
Marchetti, 2019 ⁴⁷	Retrospective cohort	SC + chemo vs chemo only	23	96 (R0)	NR	NR	OS: P=0.02
			23				

chemo, chemotherapy; DFS, disease-free survival; HR, hazard ratio; mo, months; NR, not reported; OS, overall survival; PFS, progression-free survival; SC, secondary cytoreduction.

^a Matched cohort.

^b Unmatched cohort.

sample sizes tend to be small, and a few studies in particular are limited by overfitting.^{43,46} At the end of the study performed by Chuang and colleagues, the researchers used instrumental variable methods to try to account for unmeasured covariates that might make the propensity score less robust.⁴⁴ This approach revealed that true treatment effects may approach the null hypothesis if the association between unmeasured confounders and disease outcomes is strong. A closer evaluation of the variables led the authors to define tumor burden at recurrence as single sites vs multiple tumor sites or carcinomatosis. However, the latter category encompasses a large spectrum of disease states, ranging from 2 isolated nodules up to extensive carcinomatosis with numerous metastases and large ascites. From other studies, we know that patients with more advanced metastases and ascites typically are receiving only chemotherapy and usually have far worse outcomes. More recently, in 2019, Gockley and colleagues analyzed a propensity-scored, matched retrospective cohort study involving 6 centers.³³ In one of their sensitivity analyses, they sought to determine if the survival advantage for SC could be explained by other unmeasured variables using HRs from Chi and colleagues.¹⁹ They discovered that the differences could be explained if multifocal recurrence was 4.3 times more common, ascites was 2.7 times more common, or carcinomatosis was 2.1 times more common

among patients receiving chemotherapy alone. These variables are generally much more common among patients receiving chemotherapy alone. The rates of these characteristics among the study population were not available to the authors for analysis, and in combination could explain these survival differences.

What Is the Clinical Utility of SC? Efficacy Data From Randomized Clinical Trials

Since 2005, at least 5 RCTs that compare SC with chemotherapy have begun enrollment (Table 2). Two of these trials closed early owing to poor accrual. Only GOG-0213 has reached maturity for its primary endpoint, and the 2 other trials are ongoing.

DESKTOP III. DESKTOP III is an RCT that includes patients with epithelial ovarian cancer who had their first relapse after a platinum-free interval of at least 6 months and a positive AGO score predicting CGR-R0.⁹ Preliminary results were presented at the 2017 annual meeting of the American Society of Clinical Oncology. Patients from 80 centers in 12 countries were randomly assigned to either chemotherapy alone or secondary cytoreductive surgery followed by chemotherapy. Chemotherapy regimens were determined by the standards at each individual institution. Overall, a complete

Table 2. Results From Randomized Clinical Trials

Study	Inclusion Criteria	Primary Endpoint	Groups	N (% cross-over)	Optimal Resection, %	Median OS, mo	Median PFS, mo	HR (95% CI)
GOG-0213 ¹⁰	<ul style="list-style-type: none"> • Recurrent ovarian, primary peritoneal, or fallopian tube cancer • Complete response to primary platinum-based therapy • ≥6-month platinum-free interval • Surgical candidate based on likelihood of complete gross resection 	(1) Determine if Bev with paclitaxel/ carboplatin and as maintenance therapy improves OS (2) Determine if secondary cytoreduction followed by chemo increases OS	• SC + PBC +/- Bev	240 (10%)	67	50.6	18.9	OS: 1.29 (0.97-1.72) PFS: 0.82 (0.66-1.01)
			• PBC +/- Bev	245	(R0)	64.7	16.2	
DESK-TOP III ⁹	<ul style="list-style-type: none"> • First relapse of ovarian cancer • Complete primary cytoreduction • ≥6-month platinum-free interval • ECOG performance status 0 • Ascites ≤500 mL 	(1) Determine if SC followed by chemo increases OS relative to chemo alone	• SC + chemo	204 (6.9% no SC)	72.5	Pending	19.6	OS pending PFS: 0.66 (0.52-0.83)
			• Chemo alone	203 (8.9% SC)	(R0)		14.0	
SOC 1 ⁵¹	<ul style="list-style-type: none"> • Platinum-sensitive first relapse of ovarian, primary peritoneal, or fallopian tube cancer • Tian low-risk with integration of PET/CT analysis 	(1) Determine if SC followed by chemo increases OS relative to chemo alone (2) Determine if SC followed by chemo increases PFS relative to chemo alone	• SC + chemo	Pending	Pending	Pending	Pending	Pending
			• Chemo alone					
SOC-ceR ⁴⁹	<ul style="list-style-type: none"> • Recurrent platinum-sensitive epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer, with ≥6-month disease-free interval • ECOG performance status 0-1 • Ascites ≤500 mL • Complete resection deemed possible 	(1) Determine if interval SC followed by chemo increases PFS relative to chemo alone	<ul style="list-style-type: none"> • SC + PBC • ≥6 cycles PBC 	Study cancelled because only 27 of 230 target patients accrued over 3 years				

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Table 2. (Continued) Results From Randomized Clinical Trials

Study	Inclusion Criteria	Primary Endpoint	Groups	N (% cross-over)	Optimal Resection, %	Median OS, mo	Median PFS, mo	HR (95% CI)
LOROC-SON (EORTC-55963) ⁵²	<ul style="list-style-type: none"> • Recurrent epithelial ovarian cancer with ≥ 6-month disease-free interval • ECOG performance status 0-2 • Induction chemotherapy without progression • ≥ 4 courses of first-line PBC 	<p>(1) Determine if interval SC followed by chemo increases OS relative to chemo alone</p> <p>(2) Determine if interval SC followed by chemo increases PFS relative to chemo alone</p>	<ul style="list-style-type: none"> • Interval SC + chemo • Chemo alone 	Study cancelled for poor accrual				

Bev, bevacizumab; chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, months; OS, overall survival; PBC, platinum-based chemotherapy; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival.

resection was achieved in 72.5% of patients. PFS was 14 months without surgery and 19.6 months with surgery (HR, 0.66; 95% CI, 0.52-0.83; $P < .001$). The time to first subsequent therapy was also increased from 13.9 months in the no-surgery arm to 21 months in the surgery arm (HR, 0.61; 95% CI, 0.48-0.77; $P < .001$). OS has not yet been reported owing to study immaturity. The benefits of surgery were exclusive to patients who had a complete resection.

GOG-0213. GOG-0213 was a phase 3 RCT of secondary cytoreductive surgery followed by platinum chemotherapy with or without bevacizumab.^{10,48} The study had 2 primary objectives: (1) to determine if the addition of bevacizumab, both during treatment with paclitaxel and carboplatin and as maintenance therapy, increased OS and (2) to determine if SC followed by chemotherapy increased OS. For the second objective, the protocol provided no specific eligibility criteria for SC. With the goal of complete removal of all visible disease, the protocol provided guidance that carcinomatosis, ascites, and parenchymal organ disease suggest poor surgical candidacy. Assessment of patients permitted physical examination, laboratory evaluation, and imaging.

In the surgical component, 485 women were randomly assigned in a 1:1 ratio to cytoreduction followed by chemotherapy ($n=240$) or chemotherapy alone ($n=245$).¹⁰ The overall rate of complete gross resection was 63% overall among patients assigned to SC and 67% per protocol. OS was 50.6 months for those who underwent SC surgery compared with 64.7 months for those who did not (HR, 1.29; 95% CI, 0.97-1.72; $P=.08$). Adjustments

for the platinum-free interval and chemotherapy choice did not affect this result. PFS was similar at 18.9 months for SC and 16.2 months for no surgery (HR, 0.82; 95% CI, 0.66-1.01). Compared with patients who had a suboptimal resection, patients who had a complete gross resection had better PFS (HR, 0.51; 95% CI, 0.36-0.71) and OS (HR, 0.61; 95% CI, 0.49-0.93).

In an exploratory analysis for PFS and OS, surgical patients with a complete gross resection were compared with all patients receiving chemotherapy without surgery. As in DESKTOP III, PFS was improved by complete gross resection (HR, 0.62; 95% CI, 0.48-0.80).^{9,10} However, there was no difference in OS (HR, 1.03; 95% CI, 0.74-1.46).¹⁰

Surgery for Ovarian Cancer Recurrence (SOCceR) Trial.

The SOCceR trial was a multicenter RCT that included patients from all 9 gynecologic oncology centers within the Netherlands with recurrent epithelial ovarian cancer.⁴⁹ Participants were randomly assigned to platinum-based chemotherapy or to secondary cytoreductive surgery followed by platinum-based chemotherapy. Unfortunately, the trial closed early owing to slow accrual.⁵⁰

Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC 1) Trial.

SOC 1 is an ongoing, multicenter, randomized controlled trial that includes several cancer centers in China.⁵¹ The trial is randomly assigning women with recurrent epithelial, primary peritoneal, or fallopian tube cancer to SC plus chemotherapy or chemotherapy alone. Women must be at least 18 years of age and experiencing their first relapse after a treatment-free

interval of at least 6 months. Additionally, they must have a Tian score of 4.7 or less, or a modified score wherein CA-125 is scored as 0 if the investigators believe that the recurrent tumor detected by positron emission tomography/computed tomography could be completely resected. This trial design is promising, and the results will be invaluable. However, the study is still accruing, and the data will be affected by patients who cross over to the SC group from the chemotherapy-only group. Results have not yet been reported.

Late-Onset Recurrent Ovarian Cancer: Surgery or Not (LOROCSON). LOROCSON, also known as European Organisation for Research and Treatment of Cancer (EORTC)-55963, was a randomized phase 2 clinical trial in which patients were randomly assigned to chemotherapy alone or chemotherapy with interval SC. Enrolled patients had recurrent disease after a disease-free interval of at least 1 year. All patients received induction chemotherapy for 3 months and then, if they did not progress, were randomly assigned to 3 additional cycles of chemotherapy with or without interval SC. Although the approach was promising, the trial was closed owing to poor enrollment.⁵²

Discussion

The clinical utility of SC in recurrent ovarian cancer has evolved over time. High-level evidence has shown that PFS is improved by SC in properly selected patients. Several models have proven predictive in determining which patients are most likely to benefit from SC. Patients with longer treatment-free intervals, those with isolated tumors, and those who lack ascites and carcinomatosis appear to derive the greatest benefit in nearly all studies. The value of SC in significantly improving OS has not been substantiated in RCTs to date. Retrospective studies have shown promise, but all are limited by a lack of randomization and obvious selection bias, ensuring fundamental differences between the patients treated with SC and those treated with chemotherapy alone. Finally, although not specifically addressed, SC—like all ovarian cancer treatment—optimally should be performed at dedicated high-volume centers to maximize survival.⁵³

Although the PFS results from DESKTOP III are promising, the study is not without limitation. Although the HRs are convincing, some may debate whether *P* values have utility in secondary hypothesis testing. A significant limitation is that PFS is characterized by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.⁵⁴ RECIST criteria require a 20% increase in the sum of the longest diameter of target lesions, the appearance of 1 or more new lesions, or unequivocal progression of existing

nontarget lesions.⁵⁵ Given that after complete resection there may be no measurable disease on imaging, it might be expected that the surgical group would perform better, although without any real difference in survival, because the surgical group has a fundamentally different baseline.⁵⁶ Thus, there is artificial manipulation of this endpoint by decreasing or eliminating the target lesions. The OS data from DESKTOP III will be a critical component in assessing the value of SC, particularly relative to that reported by GOG-0213. Factors such as adjuvant therapy choice, post-progression survival, and perhaps *BRCA1/2* mutation status with associated targeted therapy will be important considerations in understanding the role of SC in patients with platinum-sensitive recurrent disease. In addition, if OS is increased with SC in DESKTOP III, then selection criteria for SC may be revisited to optimize the CGR-R0, perhaps with the inclusion of FDG-PET and laparoscopy.

Moreover, the use of bevacizumab could be fundamental in accounting for the differences in results between the 2 trials. Of note, GOG-0213 and DESKTOP III reported very similar median PFS rates in the experimental arms (18.9 and 19.6 months, respectively), with the primary difference arising from the control arms (16.2 and 14 months, respectively). PFS in the SC groups correlates well with the rate of complete gross resection, with 67% in GOG-0213 and 72.5% in DESKTOP III (67% in the abstract, 72.5% in the presentation). Altogether, these data would suggest that the difference arises from variations in the treatment regimens. Indeed, bevacizumab was used in 20% of patients in DESKTOP III compared with more than 80% in GOG-0213. If a difference in OS between the treatment arms is found in DESKTOP III, it may be explained by the lack of bevacizumab.

The present study has several strengths. It strives to be comprehensive by querying 3 databases and systematically selecting and reviewing references per PRISMA guidelines. Inclusion and exclusion criteria were not based on a priori knowledge of the literature. Conclusions within this study are founded upon a thorough and up-to-date compilation of both retrospective studies and prospective randomized clinical trials. Additionally, this systematic review identifies potential reasons for conflicting results across studies.

There were several limitations of this review. Although the chosen databases and search methods provided a substantial breadth of literature to analyze, there still could be unretrieved references. Additionally, although references were methodically evaluated using strict criteria, only a single reviewer selected references for inclusion, leading to potential reporting bias. Like all reviews, the present study may be limited by selective publication, whereby studies with less dramatic results may not have been published.

Finally, this study is only qualitative, as a meta-analysis was not performed.

Conclusions

Given the closure of the SOCcer trial, the remaining critical question will be, what if the results of DESKTOP III conflict with those of GOG-0213? If no difference in OS is identified, this will likely signify the end of SC for ovarian cancer for the foreseeable future in nearly all settings. Although the increase in morbidity associated with surgery has been small in the available studies, if there is no increase in OS in either randomized trial, it would be difficult to justify continuation of this clinical practice unless certain subgroups are found to benefit from curative intent. Alternatively, if the studies are discordant—with DESKTOP III showing statistically improved OS—2 potential arguments will arise. First, the selection bias built into GOG-0213 by the up-front declaration as to whether the patient is a surgical candidate could potentially be seen as a weakness. Second, patients in DESKTOP III who are randomly assigned to chemotherapy alone are permitted to undergo surgery following progression, leading to potential criticism of the control arm because crossover to SC could obscure any difference in OS. Regardless, if DESKTOP III demonstrates improved OS, then SC will likely continue to be utilized globally in the patient population specified in this study as we await the results of SOC 1.

Disclosures

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