GYNECOLOGY

Outcomes of secondary cytoreductive surgery for patients with platinum-sensitive recurrent ovarian cancer

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BACKGROUND: Most women with advanced epithelial ovarian cancer develop recurrent disease, despite maximal surgical cytoreduction and adjuvant platinum-based chemotherapy. In observational studies, secondary cytoreductive surgery has been associated with improved survival; however its use is controversial, because there are concerns that the improved outcomes may reflect selection bias rather than the superiority of secondary surgery.

OBJECTIVE: To compare the overall survival of women with platinum-sensitive recurrent ovarian cancer treated at National Cancer Institute–designated cancer centers who receive secondary surgery vs chemotherapy.

STUDY DESIGN: This retrospective cohort study included women from 6 National Cancer Institute–designated cancer centers diagnosed with platinum-sensitive recurrent ovarian cancer between January 1, 2004, and December 31, 2011. The primary outcome was overall survival. Propensity score matching was used to compare similar women who received secondary surgery vs chemotherapy. Additional analyses examined how these findings may be influenced by the prevalence of unobserved confounders at the time of recurrence.

RESULTS: Among 626 women, 146 (23%) received secondary surgery and 480 (77%) received chemotherapy. In adjusted analyses, patients who received secondary surgery were younger ($P = 0.001$), had earlier-stage disease at diagnosis ($P = 0.002$), and had longer disease-free intervals ($P < 0.001$) compared with those receiving chemotherapy. In the propensity score–matched groups (n = 244 patients), the median overall survival was 54 months in patients who received secondary surgery and 33 months in those treated with chemotherapy ($P < 0.001$). Among patients who received secondary surgery, 102 (70%) achieved optimal secondary cytoreduction. There were no significant differences in complication rates between the 2 groups. In sensitivity analyses, the survival advantage associated with secondary surgery could be explained by the presence of more multifocal recurrences (if 4.3 times more common), ascites (if 2.7 times more common), or carcinomatosis (if 2.1 times more common) among patients who received chemotherapy instead of secondary surgery.

CONCLUSION: Patients with platinum-sensitive recurrent ovarian cancer who received secondary surgery had favorable surgical characteristics and were likely to have minimal residual disease following secondary surgery. These patients had a superior median overall survival compared with patients who received chemotherapy, although unmeasured confounders may explain this observed difference.

Key words: chemotherapy, cytoreductive surgery, recurrent ovarian cancer

Most women with advanced epithelial ovarian cancer develop recurrent disease despite maximal surgical cytoreduction and adjuvant platinum-based chemotherapy.[1] Women with platinum-sensitive recurrent ovarian cancer (PSROC) can be treated with secondary cytoreductive surgery (SCS) and chemotherapy or chemotherapy alone. In observational studies, the use of SCS has been associated with a higher median overall survival (range, 45–61 months),[2–11] compared with chemotherapy alone (25-42 months).[12–16] The use of SCS is controversial, however, because there are limited data from randomized controlled trials[17–19], and there are concerns that the improved outcomes from observational studies may reflect selection bias rather than the superiority of SCS.

The DESKTOP I trial was an exploratory study that combined retrospective data from 25 centers in Germany and Switzerland to identify factors associated with improved survival after SCS.[2] The factors identified included the following: (1) Eastern Cooperative Oncology Group performance status (PS) of 0 vs >0; (2) lower stage at diagnosis (International Federation of Gynecology and Obstetrics (FIGO) stage I/II vs III/IV); (3) absence of residual disease after primary cytoreductive surgery; and (4) absence of ascites at the time of recurrence. DESKTOP II applied 3 of these criteria, naming them a "positive AGO-score" (PS 0, ascites <500 ml, and complete resection at initial surgery) to prospectively select patients with PSROC for SCS. Among this population of patients with a positive AGO score, 76% achieved an optimal cytoreduction.[20]

Subsequently, 3 phase III randomized controlled trials were launched to compare SCS vs chemotherapy in patients with PSROC: DESKTOP III, Gynecologic Oncology Group 213, and Surgery for Ovarian Cancer Recurrence (SOCceR). Preliminary results from DESKTOP III demonstrated that patients with a positive AGO score who were randomized to receive SCS achieved a significantly longer progression-

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AJOG at a Glance

Why was this study conducted?

Among platinum-sensitive recurrent ovarian cancer patients, the difference in overall survival associated with secondary cytoreductive surgery compared with chemotherapy alone is unknown. This study uses data from 6 National Cancer Institute–designated centers to address this question.

Key findings

Of 626 patients, 23% received secondary cytoreductive surgery, whereas 77% received chemotherapy alone. In a propensity score–matched sample, patients who received secondary cytoreductive surgery had a median overall survival of 54 vs 33 months in patients treated with chemotherapy alone ($P < 0.001$).

What does this add to what is known?

With results of randomized controlled trials forthcoming, some platinum-sensitive recurrent ovarian cancer patients with favorable risk factors may derive a significant survival benefit from secondary cytoreductive surgery.

free survival (median 19.6 months), compared with those who received chemotherapy (median 14.0 months)[17]; however, the overall survival data are not yet available. GOG 213 randomized patients with PSROC to SCS or chemotherapy alone, and notably nearly 80% of patients in each arm received bevacizumab. In preliminary data presented, there was no improvement in progression-free or overall survival.[18] SOCceR was closed prematurely due to poor enrollment.[19]

Given the conflicting evidence regarding the role of SCS, the purpose of this study was to compare the overall survival of women with PSROC who underwent SCS with those who received chemotherapy in patients who were treated at 6 NCI-designated cancer centers. Our secondary objectives were to compare the characteristics and 30-day complication rates associated with SCS, compared with chemotherapy. Given the potential role of unmeasured confounders in patient selection for SCS, we also conducted sensitivity analyses to determine the effect of unmeasured confounders on our results.

Materials and Methods

The National Comprehensive Cancer Center Network (NCCN) Ovarian Cancer Outcomes Database includes patients diagnosed with ovarian, fallopian tube, or primary peritoneal cancer between January 1, 2004, and December 31, 2012. Data were previously prospectively collected on all patients who received all or part of their care at the following 6 institutions: City of Hope Comprehensive Cancer Center; Dana-Farber/Brigham and Women's Cancer Center; Fox Chase Cancer Center; Ohio State University Comprehensive Cancer Center; The University of Texas MD Anderson Cancer Center; and the University of Michigan Comprehensive Cancer Center. Trained clinical research associates performed medical record abstraction, which, in prior studies has been shown to be reliable.[21,22] Abstracted data included sociodemographic (eg, age, race/ethnicity, income, and zip code), clinical (eg, Charlson Comorbidity Index[23] and GOG performance status), tumor (eg, stage, grade, histology, and disease sites at diagnosis and recurrence), and treatment (eg, surgical procedures and chemotherapy) characteristics, residual disease, and vital status. Patients were considered to be platinum sensitive if they had at least a 6-month treatment-free interval from the conclusion of adjuvant therapy to secondary treatment. Secondary cytoreductive surgery was defined as a surgical intervention following recurrence that included maximal cytoreduction effort and excluded procedures performed for diagnosis of recurrence or symptom management (eg, biopsy, gastric tubes, palliative colostomies, and ileostomies). As this was a retrospective multi-institution study, no uniform criteria were applied when selecting patients for secondary cytoreduction. Detailed data were collected longitudinally until death for all patients who continued to be seen at participating centers. Vital status was confirmed by the National Death Index. Patient deaths were abstracted through February 15, 2013; patients alive after this date were censored. The institutional review board at each center approved the overall project, and the Dana-Farber/Harvard Cancer Center's Office for Human Research Studies deemed this study exempt from review.

Factors associated with receipt of secondary surgery

We tested for changes in the proportion of patients receiving SCS over time using the Cochran–Armitage test for trend. We examined unadjusted associations between sociodemographic, clinical, and institutional factors associated with the receipt of SCS vs chemotherapy with χ^2 tests. Because of the limited sample size, we were unable to include all factors of interest as independent variables in a multivariable model. Therefore, we identified a subset of factors that were hypothesized to have the greatest influence on treatment, including the following: interval to recurrence, income, body mass index, Charlson Comorbidity Index, institution, year of secondary treatment, histology, grade, stage, and residual disease status. These selected factors were included as independent variables in a multivariable logistic regression model to assess independent associations with receipt of SCS vs chemotherapy.

Association between secondary treatment and overall survival using a propensity score–matched cohort

Patients who underwent SCS were matched to patients who received chemotherapy by nearest neighbor matching using a caliper of 0.2 of the pooled standard deviation of the log odds of the propensity score, which was calculated using all of the factors listed in

TABLE 1
Characteristics of patients with platinum-sensitive recurrent ovarian cancer treated with secondary cytoreductive surgery vs chemotherapy only at National Cancer Institute–designated cancer centers (2004–2012)

		Unadjusted		Adjusted		
	Overall N (column) %)	Row % receiving secondary surgery	*P* value	Odds Ratios	95% CI	*P* value
Overall	632	23				
Interval to recurrence, mo[a]			<0.001			<0.001
<12	54 (9)	15		1		
12–17	256 (41)	12		0.74	0.29, 1.85	
18–23	150 (24)	24		1.96	0.78, 4.95	
≥24	172 (27)	41		4.81	1.93, 12.01	
Age at recurrence, y[a]			0.001			0.001
18–54	165 (26)	33		1		
55–64	218 (34)	20		0.41	0.24, 0.71	
65–74	163 (26)	22		0.57	0.32, 1.01	
>74	86 (14)	13		0.23	0.10, 0.53	
Race			0.44			
White	577 (91)	23				
Nonwhite	55 (9)	27				
Ethnicity			0.03			
Non-Hispanic	608 (96)	22				
Hispanic	24 (4)	42				
Insurance			0.2			
Commercial	350 (55)	26				
Medicare	249 (39)	19				
Medicaid	19 (3)	21				
Other	14 (2)	14				
Income[a]			0.32			0.45
1 (lowest)	152 (24)	24		1		
2	154 (24)	21		1.16	0.61, 2.21	
3	173 (27)	19		0.88	0.47, 1.65	
4 (highest)	153 (24)	29		1.42	0.75, 2.68	
Body mass index			0.15			0.14
≤30	407 (64)	25		1		
>30	164 (26)	18		0.61	0.36, 1.05	
Unknown	61 (10)	23		0.63	0.28, 1.41	
Charlson Comorbidity Index at primary diagnosis			0.007			0.17
0	494 (78)	26		1		
≥1	138 (22)	14		0.67	0.37, 1.19	

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

(continued)

TABLE 1
Characteristics of patients with platinum-sensitive recurrent ovarian cancer treated with secondary cytoreductive surgery vs chemotherapy only at National Cancer Institute–designated cancer centers (2004–2012) *(continued)*

		Unadjusted		Adjusted		
	Overall N (column) %)	Row % receiving secondary surgery	*P* value	Odds Ratios	95% CI	*P* value
GOG PS at primary diagnosis			0.04			
0	437 (69)	23				
≥1	106 (17)	16				
Unknown	89 (14)	31				
Institution[b]			<0.001			0.001
1	26 (4)	46		2.61	0.95, 7.22	
2	192 (30)	27		0.96	0.50, 1.85	
3	78 (12)	6		0.2	0.07, 0.60	
4	118 (19)	28		1		
5	78 (12)	12		0.34	0.14, 0.83	
6	140 (22)	25		0.97	0.51, 1.86	
Years of secondary treatment[a]			<0.001			0.001
2003–2006	99 (16)	26		1		
2007–2008	155 (25)	32		0.94	0.49, 1.81	
2009–2010	199 (32)	24		0.59	0.31, 1.14	
2011–2012	177 (28)	13		0.28	0.13, 0.59	
Primary site			0.14			
Ovarian	506 (80)	25				
Fallopian	42 (7)	19				
Peritoneal	84 (13)	15				
Histology of primary diagnosis			0.01			0.08
Serous	468 (74)	20		1		
Nonserous	164 (26)	31		1.54	0.95, 2.48	
Grade of primary diagnosis			0.59			0.88
I	21 (3)	19		1		
II–III	566 (90)	23		1.35	0.41, 4.47	
Unknown	45 (7)	29		1.42	0.34, 5.89	
Stage of primary diagnosis			<0.001			0.002
I–IIIa/b	128 (20)	39		1		
IIIc/IV	504 (80)	19		0.44	0.26, 0.74	
CA-125 at primary diagnosis			0.2			
<35	27 (4)	26				
35–500	222 (35)	22				
>500–1000	66 (10)	27				
>1000	199 (31)	19				
Unknown	118 (19)	30				

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019. *(continued)*

TABLE 1
Characteristics of patients with platinum-sensitive recurrent ovarian cancer treated with secondary cytoreductive surgery vs chemotherapy only at National Cancer Institute–designated cancer centers (2004–2012) *(continued)*

		Unadjusted		Adjusted		
	Overall N (column) %)	Row % receiving secondary surgery	*P* value	Odds Ratios	95% CI	*P* value
Ascites at primary diagnosis			0.07			
Absent	379 (60)	26				
Present	253 (40)	19				
Residual disease at primary surgery			0.85			0.71
No residual disease or optimal	499 (79)	23		1		
Suboptimal (>1 cm)	94 (15)	21		1.21	0.64, 2.26	
Unknown	39 (6)	26		0.78	0.31, 1.96	
Receipt of neoadjuvant chemotherapy			0.001			
No	531 (84)	26				
Yes	101 (16)	10				

GOG, Gynecologic Oncology Group.

[a] *P* value calculated from test for trend across ordinal categories; [b] Institution-specific frequencies are suppressed to avoid identification of specific institutions.

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

Table 1. Survival time started on the date of SCS or the date of chemotherapy, whichever came earlier. Within the propensity score–matched cohort, survival curves were estimated using Kaplan–Meier methods. Cox proportional hazards regression was used to examine associations between treatment (ie, SCS or chemotherapy) and overall survival, with a robust variance estimator to correct for clustering within matched pairs.

Association between secondary treatment and 30-day complications

Complications were defined as events within 30 days of the date of secondary surgery or initiation of secondary chemotherapy. Within the propensity score–matched sample, the McNemar test for matched pairs was used to test for differences in 30-day complication rates between the 2 treatment groups.

Evaluating for unmeasured confounders

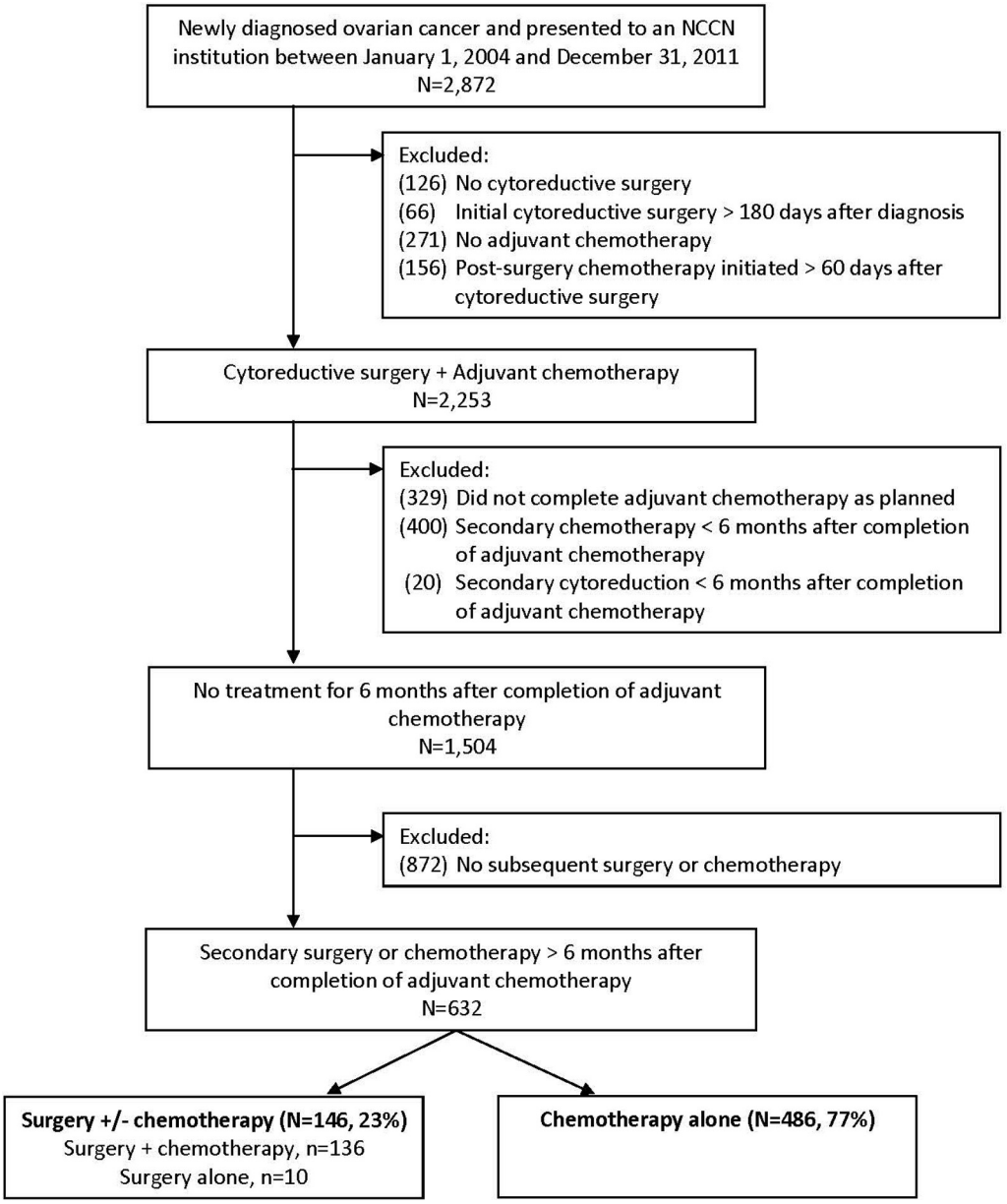
We evaluated the sensitivity of our finding to unmeasured confounding using the *E*-value approach described by Vanderwheele et al.[24] We calculated the *E* value associated with moving the point estimate and 95% confidence interval to include the null in our main analysis. We converted between rate ratios and hazard ratios (HRs) for common outcomes using the heuristic developed by Vanderwheele to compare minimum exposure–disease relationships (calculated on the rate ratio scale) with HRs reported in prior studies.[25] Specifically, we evaluated the relative prevalence of disease characteristics that would be required to explain away the association observed between SCS and overall survival in the propensity-matched analysis. The variables chosen were based on the Chi et al study, which reported the following HRs associated with increased risk of death in a SCS population: multifocal disease (HR = 1.8), ascites (HR = 2.3), and carcinomatosis (HR = 3.8).[6]

Results

Among 2872 women diagnosed with ovarian cancer at 6 NCI-designated cancer centers, there were 632 women with PSROC who received either SCS or chemotherapy >6 months after completion of their adjuvant treatment (Figure 1). Among women with PSROC, 146 (23%) underwent SCS, whereas 486 (77%) received chemotherapy alone (Table 1). Among women with PSROC, the proportion of patients who underwent SCS increased from 26% in 2004 to 32% in 2007 and then decreased to 13% in 2012 (Supplementary Figure 1). The proportion of patients who underwent SCS also varied significantly between sites (eg, from 6% to 46%, $P < 0.001$). Given the broad range of patients contributed per site (n = 26–192), these trends were not analyzed (Supplementary Figure 2).

In adjusted analyses, patients who underwent SCS were younger ($P = 0.001$), had earlier-stage disease at diagnosis ($P = 0.002$), and had longer disease-free intervals ($P < 0.001$), compared with those receiving chemotherapy (Table 1). Patients who experienced recurrence at least 24 months from completion of adjuvant treatment had increased odds of receiving SCS (adjusted odds ratio [AOR], 4.81; 95% confidence interval [CI], 1.93–12.01). Patients were also more likely to undergo SCS in earlier years compared with later years ($P = 0.001$); by 2011–2012, the AOR of receiving SCS had declined nearly 4-fold (AOR, 0.28; 95% CI, 0.13–0.59). There was no significant difference in the likelihood of receiving SCS based on the extent of residual

FIGURE 1
Flow chart of inclusion and exclusion criteria. This figures depicts the patients included in the study and provides information regarding excluded patie006Ets



Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

disease at initial surgery. Similarly, there were no statistically significant differences observed between patients receiving SCS vs chemotherapy based upon income, body mass index, Charlson Comorbidity Index, histology, or grade.

Among women who underwent SCS, 102 (70%) achieved either no evidence of disease (62 patients, 42%) or <1 cm of residual disease (40 patients, 27%). A total of 14 patients (10%) who underwent SCS had a suboptimal cytoreduction, and 30 patients (20%) did not have residual disease status recorded. Most SCS procedures were approached by laparotomy. Although the procedures varied, bowel resections were common, with 59 (41%) women undergoing a resection (small bowel, n = 20, 14%; large bowel, n = 39, 27%). Upper abdominal procedures such as diaphragmatic stripping or resection, liver resection, pancreatectomy, and splenectomy were performed rarely in secondary cytoreductive surgery (n = 29, 20%). Notably, 10% of women who had SCS were left with a colostomy or ileostomy (Table 2).

In the propensity-matched cohort, patients who underwent SCS were more likely to experience complications within 30 days of treatment initiation,

TABLE 2
Characteristics of secondary cytoreductive surgery

	Extent of residual disease at secondary surgery			
	Total	No residual disease or optimal	Suboptimal (>1 cm)	Unknown
	N (%)	n (%)	n (%)	n (%)
Overall	146	102 (70%)	14 (10%)	30 (20%)
Approach of secondary surgery				
Unknown	3 (2)	1 (1)	0	2 (7)
Other	1 (0.6)	0	0	1 (3)
Laparoscopic	5 (3)	3 (3)	0	2 (7)
Robotic	1 (0.6)	0	0	1 (3)
Laparoscopic converted to open	4 (3)	3 (3)	0	1 (3)
Laparotomy (open)	132 (90)	95 (93)	14 (100)	23 (7)
Extent of secondary surgery				
TAH, BSO, and/or omentectomy	33 (23)	16 (16)	14 (100)	3 (10)
Small bowel resection	20 (14)	15 (15)	0 (0)	5 (17)
Large bowel resection	39 (27)	27 (27)	4 (29)	8 (27)
Colostomy/ileostomy	15 (10)	6 (6)	3 (21)	6 (20)
Pelvic/para-aortic lymphadenectomy	33 (23)	25 (25)	3 (21)	5 (17)
Upper abdominal procedures	29 (20)	23 (23)	3 (21)	3 (10)
Exenterative procedures	0 (0)	0 (0)	0 (0)	0 (0)

BSO, bilateral salpingo-oopherectomy; *TAH,* total abdominal hysterectomy.
Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

compared with patients treated with chemotherapy, but none of these reached statistical significance (Table 3). Complication rates were relatively rare in both groups: anemia (3.3% vs 0.8%, p=0.38), infection (0.8% vs 0.0, $P = 0.99$), thromboembolic events (1.6% vs 0%, $P = 0.50$), cardiac or cerebrovascular event (2.5% vs 0.8%, $P = 0.63$), pneumonia or respiratory failure (1.6% vs 0%, $P = 0.50$), rehospitalization (5.7% vs 3.3%, $P = 0.51$), and intensive care unit admission (3.3% vs 0%, $P = 0.13$) were all more common among women who underwent SCS.

Within the propensity score–matched cohort, the median overall survival after initiation of secondary treatment was 54 months among patients who underwent SCS and 33 months among patients who received chemotherapy ($P < 0.001$) (Figure 2). The unadjusted HR for SCS vs chemotherapy was 0.35 (95% CI, 0.25–0.47) in favor of SCS. When examining the 122 propensity score–matched pairs alone, the HR was 0.45 (95% CI, 0.32–0.65) in favor of SCS. In the propensity score–matched analysis, SCS was associated with significant hazard reductions among patients with SCS to no evidence of disease (HR, 0.38; 95% CI, 0.23–0.64) and <1 cm of residual disease (HR, 0.59; 95% CI, 0.42–0.82) but not SCS with ≥1 cm of residual disease (HR, 0.80; 95% CI, 0.62–1.03) (Supplementary Figure 3). Patient characteristics of the propensity score matched cohort are provided in Supplementary Table 1.

In sensitivity analyses, the observed HR could be explained away by an unmeasured confounder associated with the receipt of chemotherapy (eg, carcinomatosis), instead of SCS, and an increased risk of death by a risk ratio of 2.9-fold each, but weaker confounding could not entirely explain the observed effect. On the HR scale, this corresponds to a confounder imparting at least a 2.2 times greater hazard of death. An unmeasured confounder (which was associated with SCS and death) by a risk ratio of 2.0-fold each (1.7 on the HR scale) could move the confidence interval to include the null. The observed finding could be explained by the presence of more multifocal recurrences (if 4.3 times more common), ascites (if 2.7 times more common), or carcinomatosis (if 2.1 times more common) among patients who received chemotherapy, compared with those who underwent SCS.

Comment

Principal findings

In this retrospective study of SCS at 6 NCI-designated comprehensive cancer

TABLE 3
Complication rates within 30 days of secondary treatment

	Unadjusted		Propensity score matched sample			
	Secondary SCS	Chemotherapy	Secondary SCS	Chemotherapy		
	n = 146	n = 486	n = 122	n = 122		
	Column %	Column %	Column %	Column %	Absolute difference (95% CI)	*P* value
Anemia	2.7	1.0	3.3	0.8	2.5 (−1.1 to 6.1)	0.38
Infection	1.4	0.8	0.8	0.0	0.8 (−0.8 to 2.4)	0.99
Venous thrombosis or embolus	1.4	0.4	1.6	0.0	1.6 (−0.6 to 3.9)	0.50
Anastomotic or vaginal leak	1.4	0.0	1.6	0.0	1.6 (−0.6 to 3.9)	0.50
Cardiac/CVA event	2.1	0.8	2.5	0.8	1.7 (−1.6 to 4.9)	0.63
Pneumonia, respiratory failure	1.4	0.2	1.6	0.0	1.6 (−0.6 to 3.9)	0.50
Hospitalization	4.8	3.5	5.7	3.3	2.5 (−2.4 to 7.5)	0.51
Admission to ICU	2.7	0.2	3.3	0.0	3.3 (0.1 to 6.4)	0.13

CI, confidence interval; *CVA*, cerebrovascular accident; *ICU*, intensive care unit; *SCS*, secondary cytoreductive surgery.

Complications were assessed within 30 days after the date of SCS or initiation of second-line chemotherapy. *P* values were determined by an exact McNemar test for matched pairs.

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

centers, 23% of patients with PSROC underwent SCS between 2004 and 2012. Patients who were younger, who were at earlier stages of the disease, and who experienced at least a 24-month interval to recurrence were more likely to undergo SCS. Among patients who underwent SCS, 70% achieved a cytoreduction to 0 or <1 cm of residual disease. Complication rates were low and did not differ significantly between patients who had SCS and chemotherapy, although 10% of women who had SCS were left with a colostomy or ileostomy. The median overall survival was greater in patients undergoing SCS compared with chemotherapy (54 vs 33 months, $P < 0.001$). Specifically, SCS was associated with significant hazard reductions among patients with SCS to no evidence of disease (HR, 0.38; 95% CI, 0.23−0.64) and <1 cm of residual disease (HR, 0.59; 95% CI, 0.4−0.82) but not SCS with ≥1 cm of residual disease (HR, 0.80; 95% CI, 0.62−1.03). These findings imply that SCS is safe and may confer a significant survival benefit for some women with PSROC.

Study comparison

Several prior observational studies have demonstrated that women with recurrent ovarian cancer may derive a significant benefit from SCS, particularly if there is no residual disease at the conclusion of surgery.[3,6,8,26-30] However, few researchers have directly compared the outcomes of recurrent ovarian cancer patients who treated with SCS to women treated with chemotherapy alone.[7,31] The largest study to compare these 2 treatments to date is a single-institution, retrospective Norwegian study that documented dramatic survival differences by treatment modality and residual disease. In this study, the median overall survival of patients treated with chemotherapy was 13.2 months, whereas women who underwent SCS to no residual disease had a median overall survival of 4.5 years, those with <2 cm of residual disease had a median survival of 2.3 years, and those with >2 cm lived a median of 8.4 months.[7] Unfortunately, this study included a heterogenous sample of patients, including patients who underwent SCS for early recurrences (ie, 0−5 months after treatment) and palliative surgeries (eg, for bowel obstructions), which does not reflect current practice. Our study extends this earlier work by examining a more homogenous population of women with PSROC from 6 institutions whose clinical characteristics match the eligibility criteria of ongoing randomized clinical trials, offering a window into "real-world" clinical practice at academic centers.

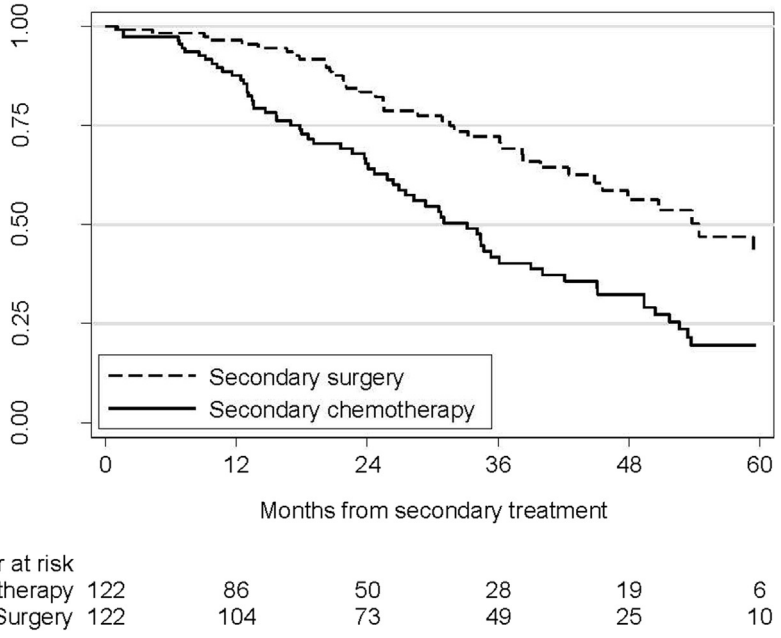
Clinical implications

The propensity score matching in the current study further extends earlier observational studies by comparing similar patients in both the SCS and chemotherapy arms. The survival analysis from this study suggests that patients with PSROC who undergo SCS may have significantly improved survival, compared with similar patients who receive chemotherapy alone at the time of recurrence. Until results from randomized trials are published, these results may inform clinical decision making for women with PSROC.

Indeed, data from 2 randomized controlled trials comparing SCS and chemotherapy have yielded conflicting results. Early evidence from DESKTOP III suggests that patients treated with SCS had superior progression-free survival compared with patients treated with chemotherapy alone (median 19.6 months vs median 14.0 months; HR, 0.66; 95% CI, 0.52−0.83), and an increased treatment-free interval (median, 21.0 vs 13.9 months; HR, 0.61; 95% CI, 0.48−0.77).[17] However, the overall

FIGURE 2

Propensity score–matched sample: overall survival (OS) by treatment for recurrence. With a median follow-up for survivors of 24 months, there were 42 deaths among patients treated with secondary cytoreductive surgery (SCS) vs 66 deaths among patients treated with secondary chemotherapy. Median survival from the date of secondary treatment was 54 months among patients receiving SCS vs 33 months among patients receiving secondary chemotherapy



Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

survival data are not yet mature. Conversely, early data from GOG-213 demonstrate no significant difference in progression-free survival between SCS and chemotherapy (18.2 vs 16.5 months; HR, 0.88; 95% CI, 0.70–1.11) or overall survival (median overall survival, 53.6 months vs 65.7 months; HR, 1.28; 95% CI, 0.92–1.78).[18] Notably, all patients in GOG-213 were eligible to receive chemotherapy with or without bevacizumab, and more than 80% received bevacizumab. Although it is difficult to ascertain the effect that bevacizumab may have had on the study results, its use may have reduced a potential survival benefit associated with SCS. Moreover, although randomized clinical trials are the ideal design for limiting bias, these studies suffered from early slow accrual—perhaps reflecting providers' reluctance to randomize patients who appeared amenable to SCS (eg patients with isolated, remote recurrences)—and the SOCceR trial closed prematurely due to poor enrollment.[19]

Research implications

This study suggests that there may be patients who benefit from SCS. Further research, including ongoing clinical trials, should prioritize identifying patient and disease factors associated with improved overall survival among patients undergoing SCS.

Strengths and limitations

Although this study combines granular data from 6 NCI-designated cancer centers and controls for multiple observed confounders, there may be unobserved factors (eg location of recurrence, ascites, carcinomatosis, the availability of consultant surgeons) that could explain our results, as demonstrated by our sensitivity analyses.[32,33] Despite this, the 70% optimal cytoreduction rate and the significantly improved overall survival that we observed with SCS, compared with chemotherapy, suggest that clinicians and surgeons in "real-world practice" may be selecting appropriate patients for SCS at these 6 centers. Although complication rates did not differ significantly between patients receiving SCS and chemotherapy, we were likely underpowered to detect significant differences given infrequent events. Despite this, the complication rates that we observed are comparable to those reported in other SCS series.

Conclusion

In this study of women with PSROC, patients who underwent SCS had superior median overall survival compared with patients who were treated with chemotherapy alone, suggesting that some patients may derive significant benefit from SCS. Until mature data from DESKTOP III and GOG 213 are published, clinicians may consider secondary cytoreductive surgery in patients with PSROC and favorable risk factors. ■

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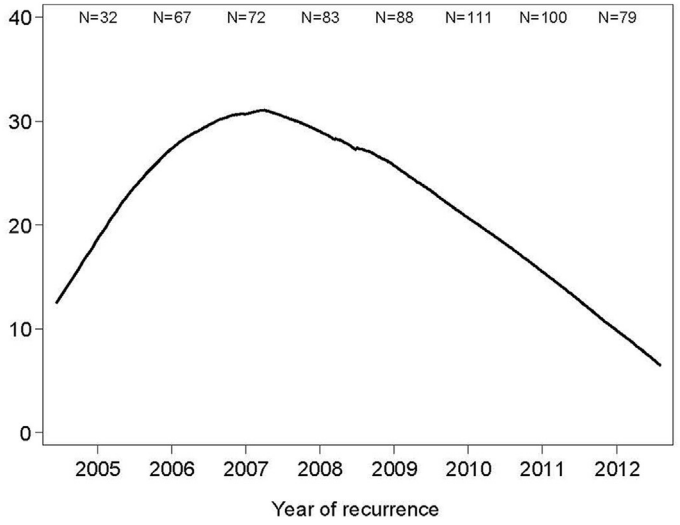
Supplementary Material

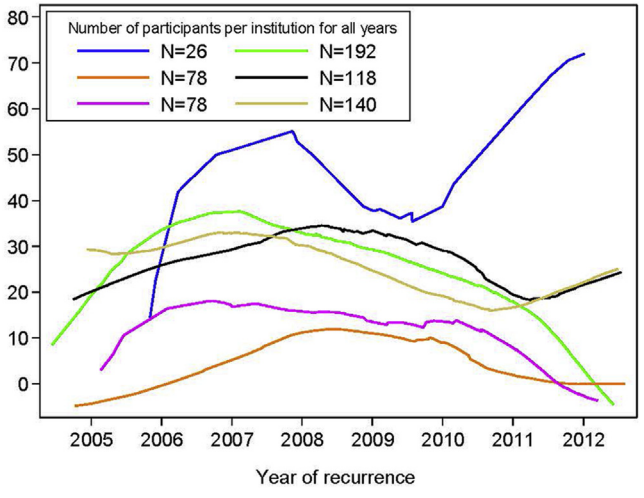
SUPPLEMENTARY FIGURE 1
Proportion of patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery (SCS) during study period. The proportion of patients with recurrent ovarian cancer treated with SCS during the study period increased from 2005 to 2007 but then decreased from 2007 to 2012 (P_{trend} = 0.001)



*Only 1 patient in the cohort had a recurrence in 2004 and she is included in the participant count for 2005; similarly, 2 patients who had a recurrence in 2013 are included in the participant count for 2012.

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 2
Institution-specific proportion of recurrent ovarian cancer patients treated with secondary cytoreductive surgery (SCS) vs chemotherapy alone at National Cancer Institute (NCI)–designated cancer centers (2004–2012). This figure depicts the patients contributed by each NCI-designated site as well as the trend in SCS over the study period within each institution



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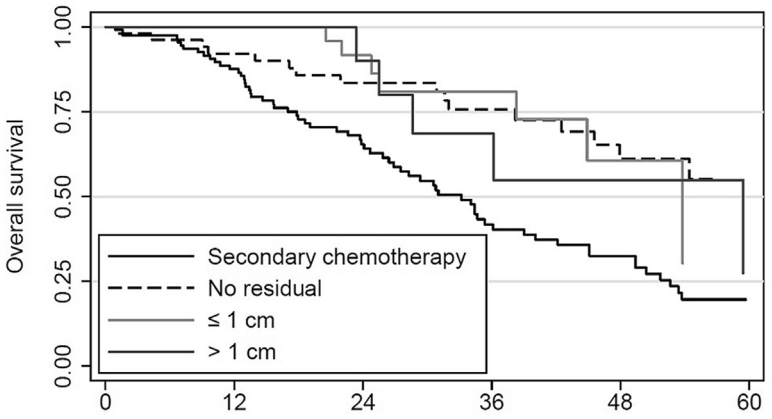
SUPPLEMENTARY FIGURE 3

Propensity score–matched sample of overall survival stratified for residual disease following secondary cytoreductive surgery (SCS) as compared to chemotherapy. In this analysis, SCS was associated with significant hazard reductions among patients with SCS to no evidence of disease (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.23–0.64) and <1 cm of residual disease (HR, 0.59; 95% CI, 0.42–0.82) but not those with ≥1 cm of residual disease after SCS (HR, 0.80; 95% CI, 0.62–1.03)



Number at risk						
Chemotherapy	122	86	50	28	19	6
No residual	53	43	35	26	15	7
≤ 1 cm	32	29	18	11	4	1
> 1 cm	12	12	9	5	2	1

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SUPPLEMENTARY TABLE 1

Patient characteristics in propensity score–matched cohort. This table displays the characteristics used in the propensity score–matched cohort

	Secondary surgery	Secondary chemotherapy
	N (%)	N (%)
Interval to recurrence (months)		
<12	7 (6)	6 (5)
12-17	30 (25)	32 (26)
18-23	32 (26)	33 (27)
≥24	53 (43)	51 (42)
Age at recurrence (years)		
18 to 54	37 (30)	43 (35)
55 to 64	41 (34)	39 (32)
65 to 74	33 (27)	29 (24)
> 74	11 (9)	11 (9)

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019. (continued)

SUPPLEMENTARY TABLE 1

Patient characteristics in propensity score–matched cohort. This table displays the characteristics used in the propensity score–matched cohort *(continued)*

	Secondary surgery	Secondary chemotherapy
Race		
White	111 (91)	109 (89)
Non-white	11 (9)	13 (11)
Ethnicity		
Non-Hispanic	117 (96)	114 (93)
Hispanic	5 (4)	8 (7)
Insurance		
Commercial	74 (61)	74 (61)
Medicare	44 (36)	46 (38)
Medicaid	2 (2)	1 (1)
Other	2 (2)	1 (1)
Income		
1 (lowest)	29 (24)	27 (22)
2	25 (20)	23 (19)
3	29 (24)	30 (25)
4 (highest)	39 (32)	42 (34)
BMI		
≤30	85 (70)	87 (71)
>30	26 (21)	27 (22)
Unknown	11 (9)	8 (7)
Charlson Index at primary diagnosis		
0	104 (85)	103 (84)
≥1	18 (15)	19 (16)
GOG PS at primary diagnosis		
0	88 (72)	93 (76)
1-2	12 (10)	12 (10)
Unknown	22 (18)	17 (14)
Institution		
1	7 (6)	5 (4)
2	44 (36)	50 (41)
3	5 (4)	4 (3)
4	27 (22)	30 (25)
5	9 (7)	8 (7)
6	30 (25)	25 (20)

Gockley et al. Secondary cytoreductive surgery for recurrent ovarian cancer. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 1

Patient characteristics in propensity score–matched cohort. This table displays the characteristics used in the propensity score–matched cohort *(continued)*

	Secondary surgery	Secondary chemotherapy
Year of secondary treatment		
2003-2006	23 (19)	27 (22)
2007-2008	40 (33)	34 (28)
2009-2010	40 (33)	32 (26)
2011-2012	19 (16)	29 (24)
Primary site		
Ovarian	102 (84)	103 (84)
Fallopian	7 (6)	6 (5)
Peritoneal	13 (11)	13 (11)
Histology of primary diagnosis		
Serous	82 (67)	81 (66)
Non-serous	40 (33)	41(34)
Grade of primary diagnosis		
I	4 (3)	7 (6)
II-III	107 (88)	107 (88)
Unknown	11 (9)	8 (7)
Stage of primary diagnosis		
I-IIIa/b	37 (30)	35 (29)
IIIc/IV	85 (70)	87 (71)
CA-125 at primary diagnosis		
<35	6 (5)	5 (4)
35-500	41 (34)	40 (33)
>500-1000	15 (12)	12 (10)
>1000	31 (25)	36 (30)
Unknown	29 (24)	29 (24)
Ascites at primary diagnosis		
Absent	78 (64)	78 (64)
Present	44 (36)	44 (36)
Residual disease at primary surgery		
No residual disease or optimal	99 (81)	95 (78)
Suboptimal (>1cm)	15 (12)	21 (17)
Unknown	8 (7)	6 (5)
Receipt of neoadjuvant chemotherapy		
No	113 (93)	108 (89)
Yes	9 (7)	14 (11)

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