GYNECOLOGY

Serial cytoreductive surgery and survival outcomes in recurrent adult-type ovarian granulosa cell tumors

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BACKGROUND: Few studies have evaluated the role of cytoreductive surgery in patients with recurrent adult granulosa cell tumors of the ovary. Despite a multitude of treatment modalities in the recurrent setting, the optimal management strategy is not known. Cytoreductive surgery offers an attractive option for disease confined to the abdomen/pelvis. However, few studies have evaluated the role of surgery compared with systemic therapy alone following the first recurrence and subsequent disease progressions.

OBJECTIVE: This study aimed to determine the impact of secondary, tertiary, and quaternary cytoreductive surgery on survival outcomes in recurrent adult granulosa cell tumors of the ovary.

STUDY DESIGN: This is a multicenter, retrospective cohort study evaluating patients with recurrent adult granulosa cell tumors of the ovary enrolled in the MD Anderson Rare Gynecologic Malignancy Registry from 1970 to 2022. Study inclusion criteria consisted of histology-proven recurrent disease, at least 1 documented recurrence, and treatment/treatment planning at the MD Anderson Cancer Center or Lyndon B. Johnson General Hospital. The primary exposure was cytoreductive surgery, and the outcomes of interest were progression-free survival and overall survival. Survival analyses were restricted to eligible patients with resectable disease without medical barriers to surgery at each progression episode. Demographic and clinicopathologic characteristics were summarized using descriptive statistics. Progression-free survival (after first, second, and third progression) and overall survival were estimated with methods of Kaplan and Meier, and were modeled via Cox proportional hazards regression. Multivariable analyses were performed for progression-free survival after first progression and overall survival.

RESULTS: Among the 369 patients with adult granulosa cell tumors of the ovary in the registry, 149 patients met the study inclusion criteria. Secondary cytoreductive surgery was associated with a significant improvement in progression-free survival on univariable (hazard ratio, 0.37; 95% confidence interval, 0.17−0.81, *P*=.01) and multivariable analyses (hazard ratio, 0.42; 95% confidence interval, 0.19−0.92; *P*=.03). Those who underwent secondary cytoreductive surgery had a significantly improved median overall survival compared with those who did not undergo cytoreductive surgery (181.92 vs 61.56 months, respectively; *P*=.002). Overall survival benefit remained statistically significant on multivariable analysis (hazard ratio, 0.28; 95% confidence interval, 0.11−0.67; *P*=.004). Tertiary cytoreductive surgery was similarly associated with a significant improvement in progression-free survival (hazard ratio, 0.43; 95% confidence interval, 0.26−0.70; *P*=.001). Despite a similar trend, quaternary cytoreductive surgery was not associated with a significant improvement in progression-free survival (hazard ratio, 0.74; 95% confidence interval, 0.42−1.26; *P*=.27).

CONCLUSION: Among those with resectable disease and no medical contraindications to surgery, cytoreductive surgery may have a beneficial impact on progression-free survival and overall survival in patients with recurrent adult granulosa cell tumors of the ovary.

Key words: cohort studies, granulosa cell tumor of the ovary, gynecologic oncology, ovarian neoplasms, surgery, survival, tumor cytoreduction

Introduction

Adult-type granulosa cell tumors of the ovary (aGCT) are rare tumors that represent 3% to 5% of all ovarian malignancies but comprise most (70%) of sex cord−stromal tumors.[1,2] Afflicted patients will typically present with early-stage disease and are treated with upfront surgery with or without adjuvant therapy.[1,3] Outcomes of frontline management for early-stage aGCT are quite favorable, with 5-year overall survival rates over 90%.[1,3,4] Despite many patients achieving long-term, disease-free survival, aGCT requires continued surveillance because the disease process follows an indolent course, and relapses have been detected more than a decade after clinical remission.[4,5] The median time to recurrence for patients with aGCT is 4 to 6 years following initial diagnosis.[6] In the recurrent setting, there are multiple treatment modalities that have been reported in the literature.[1,7] However, the optimal treatment strategy remains unknown.[7]

Given the indolent nature and recurrence patterns of aGCT, tumor cytoreductive surgery (CRS) presents an appealing management approach for recurrent aGCT. Sites of recurrent disease are generally limited to the pelvis and abdomen.[6,8,9] In a multicenter, retrospective study (MITO-9), investigators reported no cases (0 of 35) of recurrent aGCT with distant metastases; 94% of these patients had CRS for their first recurrence.[10] Similarly, other studies have demonstrated recurrent disease confined to the abdominopelvic cavity with optimal CRS rates of >80%.[8,9] Despite expert opinion support for CRS in many cases of first recurrence of aGCT, few studies have evaluated the clinical benefit of secondary CRS compared with systemic treatment alone.[7,11] Importantly, previous studies

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AJOG at a Glance

Why was this study conducted?

Few studies have evaluated the role of cytoreductive surgery compared with systemic therapy alone in recurrent adult-type granulosa cell tumors of the ovary.

Key findings

In a retrospective cohort of 149 patients with recurrent adult-type granulosa cell tumors of the ovary (with resectable disease and without surgical contraindications), secondary cytoreductive surgery was associated with a significant improvement in progression-free survival (hazard ratio [HR], 0.37) and overall survival (HR, 0.28). Tertiary cytoreductive surgery was associated with progression-free survival (HR, 0.43).

What does this add to what is known?

When tumor resection is feasible in patients without contraindications to surgery, cytoreductive surgery may be associated with improved survival in recurrent adult-type granulosa cell tumors of the ovary.

that have evaluated the role of CRS in recurrent aGCT have been subject to selection bias (eg, patients with poor performance status or comorbidities who did not undergo CRS were included into the cohort), thus markedly confounding the impact of CRS on survival outcomes.[7,12–15] Furthermore, data regarding the impact of additional lines of CRS (eg, tertiary or quaternary) on survival outcomes are limited.

The study objectives were to determine the impact of secondary, tertiary, and quaternary CRS on survival outcomes compared with systemic therapy alone. We hypothesized that patients who underwent CRS would have greater survival compared with those who received systemic therapy without CRS.

Materials and Methods

Patient population

In this retrospective cohort study, we reviewed all patients with aGCT who were enrolled in an institutional review board (IRB)–approved Rare Gynecologic Malignancy Registry (PA17-0586). In brief, this tumor registry was established at MD Anderson Cancer Center with the purpose of cataloging information regarding patients with rare tumors of the female reproductive system who were treated or received treatment planning at MD Anderson. This registry contains information related to their diagnosis, treatment course, surveillance and recurrence patterns, and disease outcomes. Among the rare ovarian tumors, this registry includes patients diagnosed with malignant germ cell, sex cord–stromal, rare epithelial (carcinosarcoma, clear cell, mucinous), and neuroendocrine tumors. Each patient's tumor histology was reviewed by 2 expert gynecologic pathologists. For this registry, patients were accrued retrospectively from January 1970 and will be prospectively accrued through January 2027. The specific analyses reported here were IRB-approved (2020-1156). To evaluate the study objectives, the inclusion criteria were as follows: patients who had histology-proven diagnosis of aGCT or granulosa cell tumor not otherwise specified (GCT NOS), at least 1 documented recurrence, and receiving or planning treatment at MD Anderson or Lyndon B. Johnson General Hospital, a county hospital affiliated with MD Anderson Gynecologic Oncology Faculty. Patients with mixed ovarian histology were included if there was an aGCT component as the driving histology in the recurrence episodes (biopsy-proven). Study exclusion criteria were as follows: disease refractory to frontline treatment, mixed histologies with other non-aGCT histology driving disease progression, and no documented follow-up after the first consultation visit.

Data collection

Study data were collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN) electronic data capture tools hosted at MD Anderson.[16,17] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. The data collection cutoff date for the present study was October 1, 2022. The following clinical and demographic data were extracted from the registry: age, stage, race/ethnicity, treatment center, tumor histology, cancer treatment history (surgical and medical management in the frontline and recurrent setting), recurrence patterns/history, and vital status. This study was conducted according to the guidelines of the Declaration of Helsinki and received IRB approval (Protocol 2020-1156). All patients provided written informed consent for the tumor registry or had a waiver of informed consent if they had not been seen at MD Anderson or Lyndon B. Johnson Hospital for at least 3 years or were deceased.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. We estimated progression-free survival (PFS) beyond the initial recurrence. PFS after the first recurrence (PFS2) was defined as the date from first recurrence to progression or death, whichever came first. Patients who were alive and known to not have progression were censored at the last clinic visit. PFS following second (PFS3) and third (PFS4) progression were similarly defined. PFS2, PFS3, and PFS4 were estimated with the methods of Kaplan and Meier and modeled via Cox proportional hazards regression. Overall survival (OS) was defined from the date

of first progression to death. Patients who were still alive were censored at the date of last contact. To evaluate effect of CRS at the time of progression on survival outcomes, univariable analyses were performed for PFS2, PFS3, PFS4, and OS. Multivariable analyses were performed for PFS2 and OS adjusting for age (<60 vs ≥60 years), administration of chemotherapy for the first progression (no vs yes), and previous adjuvant therapy in frontline management (no vs yes). Univariable and multivariable analyses were performed among those with resectable disease at the time of disease progression. Resectable disease was defined as the absence of metastases to the lung, brain/central nervous system, and bones, and insignificant liver parenchymal involvement at the time of the respective progression. Furthermore, those who were deemed medically unfit for surgery (eg, medical comorbidities or poor performance status) or had unknown resectability status before surgery were excluded from the respective PFS and OS analyses. These patients were identified, and their surgical eligibility status was evaluated through a detailed medical chart review by 2 independent reviewers (J.A.H and A.F.L). Nonconcordant results were arbitrated by a third reviewer (R.T.H). Per survival analysis, the remaining study population consisted of only patients without medical or surgical contraindications to CRS, thereby minimizing selection bias. Among patients who underwent CRS, the impact of residual disease at CRS on PFS and OS was evaluated. All *P* values were 2-sided and considered statistically significant if $P<.05$; 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using Stata/MP, version 17.0 (StataCorp LLC, College Station, TX).

Results

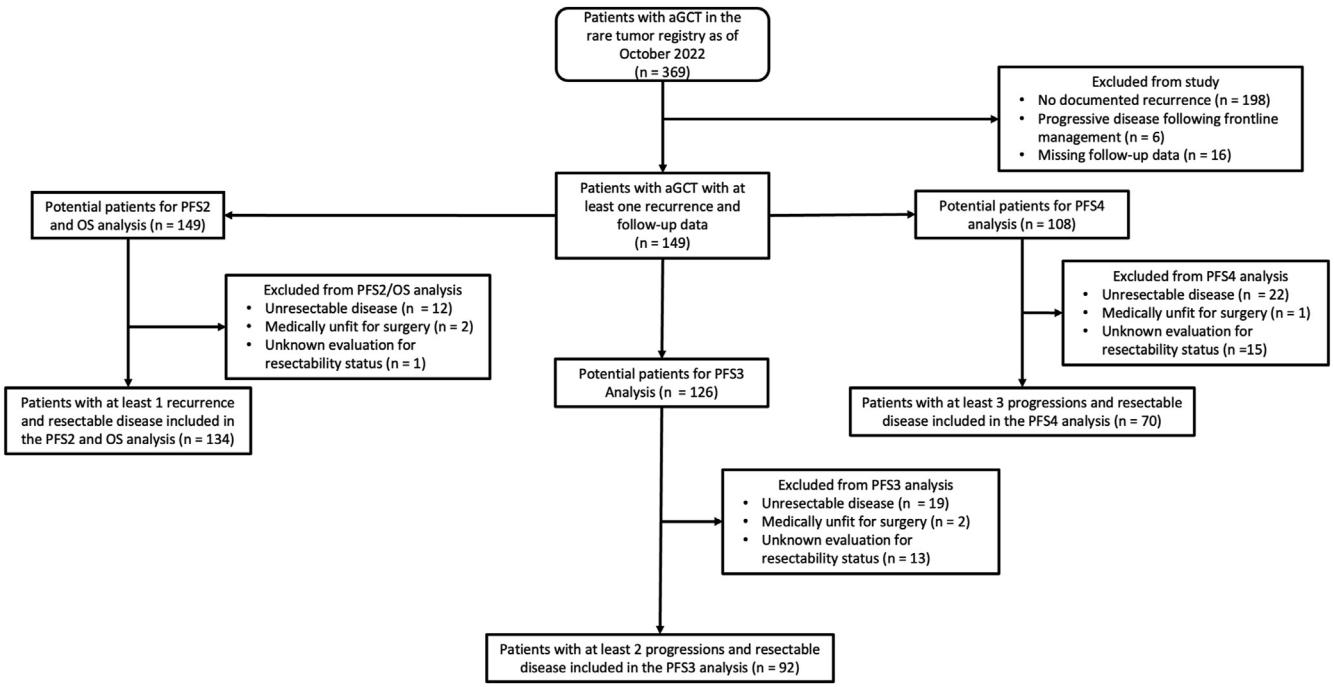
Patient population

Figure 1 demonstrates the study flow diagram. There were 369 patients who had a diagnosis of aGCT or GCT NOS in the rare tumor registry from January 1, 1970 to October 1, 2022. Among these patients, 220 patients were excluded from the analysis (198 had no documented recurrence, 6 had disease refractory to frontline treatment, and 16 had missing follow-up data), with 149 patients who met the inclusion criteria remaining for the study analysis. Among the 149 patients, the first documented progression ranged from September 1986 to December 2021. Demographic and clinical characteristics are demonstrated in Table 1. At the first documented progression, the median age was 52.62 years (interquartile range, 40–60.9) and median time to first progression from diagnosis was 50.20 months (95% CI, 45.17–63.70). The median follow-up time for all patients was 71.04 months (interquartile range, 41.04–159.60).

Survival outcomes among the overall study population

Following the first progression, there were 126 (85%) patients who had a

FIGURE 1
Flow diagram



aGCT, adult-type granulosa cell tumor of the ovary; *OS*, overall survival; *PFS2*, progression-free survival after first recurrence; *PFS3*, progression-free survival after second recurrence/progression; *PFS4*, progression-free survival after third recurrence/progression.

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TABLE 1
Demographic and clinical characteristics of the study population (n = 149)

Characteristic	n (%)
Age at the time of diagnosis (y)	
Mean (SD)	44.36 (12)
Median (IQR)	45.00 (45–54)
Age at first documented progression (y)	
Mean (SD)	50.98 (13)
Median (range)	52.62 (40–60.9)
Stage	
I	81 (74)
II	16 (15)
III	12 (11)
Unknown	40 (NA)
Histology	
Adult-type granulosa cell tumor[a]	135 (91)
Mixed[b]	14 (9)
Frontline adjuvant treatment	
None	103 (70)
Chemotherapy alone	39 (26)
Hormonal therapy alone	5 (3)
Chemotherapy and hormonal therapy	2 (1)
Race	
White	108 (74)
Black/African American	24 (17)
Asian/Native Hawaiian or other Pacific Islander	6 (4)
Other	7 (5)
Unknown	4 (NA)
Primary institution	
MD Anderson Cancer Center	147 (99)
LBJ	2 (1)
Treatment modalities through disease course	
Cytoreductive surgeries[c]	2 (1–3)
Lines of chemotherapy[c]	2 (1–3)
Lines of hormonal therapy[c]	2 (1–3)
Lines of targeted therapy[c]	0 (0–1)
Lines of radiotherapy[c]	0 (0–1)

International Federation of Gynecology and Obstetrics (FIGO) 2009 staging at time of diagnosis.

IQR, interquartile range; *LBJ*, Lyndon B. Johnson General Hospital; *NA*, not applicable.

[a] Includes adult granulosa cell tumor and granulosa cell tumor not otherwise specified; [b] Juvenile granulosa cell tumor (n=6), Sertoli-Leydig tumor (n=4), juvenile granulosa cell tumor/Sertoli-Leydig tumor (n=1), and sex cord tumor with annular tubules (n=3); [c] Represented as median (IQR).

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second progression, 108 (72%) who had a third progression, and 89 (60%) who had a fourth progression. Among all 149 patients, median PFS2 was 25.68 months (95% CI, 17.76–31.92). Among those with a second progression, median PFS3 was 13.92 months (95% CI, 10.56–16.44). Among those with a third progression, median PFS4 was 12.48 months (95% CI, 10.80–17.88). Overall, median OS was 169.8 months (95% CI, 146.52–208.32). The Supplemental Figure demonstrates the Kaplan–Meier curves stratified by CRS status among all patients.

Survival outcomes among patients with resectable disease

Figure 1 demonstrates the flow diagram for selection of patients for the survival analyses. Univariable analyses and respective Kaplan–Meier curves for PFS2, PFS3, and PFS4 are demonstrated in Table 2 and Figure 2. Among the 149 patients who had a first progression, 134 patients had resectable disease. Secondary CRS was performed in 127 patients, and 7 patients received medical recommendation for systemic therapy. Treatment regimens for patients with resectable disease at the time of progression or after CRS are shown in Supplemental Table 1. Surgical approaches/procedures performed for those who underwent CRS are shown in Supplemental Table 2. Those who underwent secondary CRS had a significant improvement in median PFS2 compared with those who did not undergo secondary CRS (31.80 vs 13.56 months, respectively; hazard ratio [HR], 0.37; 95% CI, 0.17–0.81; P=.01) (Figure 2, A). Those with no gross residual disease at the time of secondary CRS had the highest median PFS2, followed by those with gross residual disease ≤1 cm and gross residual disease >1 cm (39.24 vs 15.00 vs 10.32 months; P=.007).

Among the 126 patients with a second progression, there were 92 patients with resectable disease. Tertiary CRS was performed in 64 patients, and 28 received systemic therapy due to

TABLE 2
Univariable model for progression-free and overall survival among patients with resectable disease

	PFS2			PFS3			PFS4			OS		
Characteristic[a]	n	HR (95% CI)	*P* value	n	HR (95% CI)	*P* value	n	HR (95% CI)	*P* value	n	HR (95% CI)	*P* value
Age (y)												
<60	97	Ref		62	Ref		45	Ref		97	Ref	
≥60	37	1.34 (0.90–2.01)	.15	30	0.90 (0.56–1.44)	.66	25	0.72 (0.42–1.23)	.23	37	1.94 (1.11–3.39)	.02
CRS												
No	7	Ref		28	Ref		23	Ref		7	Ref	
Yes	127	0.37 (0.17–0.81)	.01	64	0.43 (0.26–0.70)	.001	47	0.74 (0.44–1.26)	.27	127	0.29 (0.12–0.68)	.004
Residual disease												
R0	51	Ref		28	Ref		18	Ref		51	Ref	
R≤1 cm	19	2.57 (1.36–4.85	.003	9	0.97 (0.43–2.19)	.94	7	1.10 (0.42–2.90)	.84	19	2.40 (0.78–7.38)	.13
R>1 cm	5	2.43 (0.72–5.85)	.18	2	0.93 (0.44–1.98)	.86	2	41.05 (3.57–472)	.003	5	4 (0.82–19.46)	.09
Unknown	52	NA	NA	25	NA	NA	20	NA	NA	52	NA	NA
Chemotherapy												
No	53	Ref		52	Ref		53	Ref		53	Ref	
Yes	81	1.18 (0.80–1.75)	.39	40	0.88 (0.57–1.36)	.56	17	0.99 (0.55–1.78)	.98	81	1.62 (0.94–2.81)	.08
Targeted therapy												
No	131	Ref		111	Ref		60	Ref		131	Ref	
Yes	3	2.22 (0.69–7.11)	.18	5	1.55 (0.62–3.89)	.35	10	1.41 (0.69–2.89)	.35	3	17.94 (3.58–89.9)	<.001
Radiotherapy												
No	124	Ref		115	Ref		66	Ref		124	Ref	
Yes	10	0.69 (0.33–1.41)	.31	4	1.51 (0.55–4.17)	.42	4	1.23 (0.38–3.94)	.73	10	0.76 (0.30–1.92)	.57
Hormonal therapy												
No	100	Ref		55	Ref		31	Ref		100	Ref	
Yes	34	0.80 (0.51–1.26)	.34	37	0.92 (0.59–1.44)	.72	39	0.51 (0.30–0.86)	.01	34	0.87 (0.42–1.77)	.70

CI, confidence interval; *CRS*, cytoreductive surgery; *HR*, hazard ratio; *NA*, not applicable; *OS*, overall survival; *PFS2*, progression-free survival after first recurrence; *PFS3*, progression-free survival after second recurrence/progression; *PFS4*, progression-free survival after third recurrence/progression; *Ref*, reference; *R0*, no gross residual disease present at end of cytoreduction; *R≤1*, gross residual disease ≤1 cm present at end of cytoreduction; *R>1 cm*, gross residual disease >1 cm present at end of cytoreduction.

[a] Characteristic at the time of respective disease progression.

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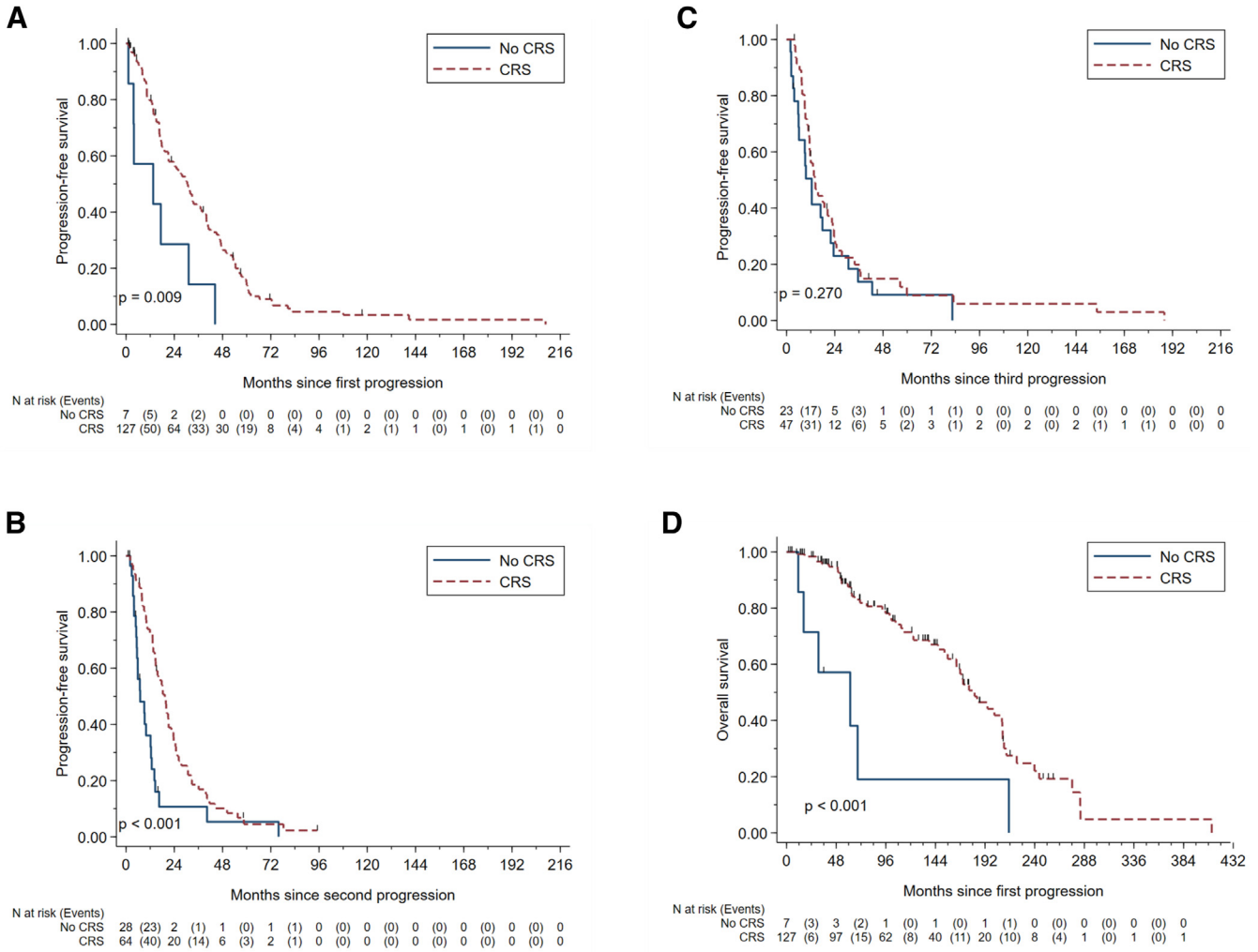
FIGURE 2
Progression-free and overall survival among patients with resectable disease



Kaplan–Meier survival curves for progression-free survival and overall survival among patients with resectable disease. **A,** Progression-free survival following first recurrence (PFS2). **B,** Progression-free survival following second progression (PFS3). **C,** Progression-free survival following third progression (PFS4). **D,** Overall survival (OS).

CRS, cytoreductive surgery.

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medical recommendation (n=26) or patient choice (n=2). Among the 64 patients with tertiary CRS, 59 previously had secondary CRS (92%). Those who underwent tertiary CRS had a significant improvement in median PFS3 compared with those who did not undergo tertiary CRS (19.32 vs 7.08 months; HR, 0.43; 95% CI, 0.26–0.70; *P*=.001) (Figure 2, B; Table 2). There was no difference in median PFS3 based on gross residual disease status (*P*=.96).

Among the 108 patients with a third progression, there were 70 patients with resectable disease. Quaternary CRS was performed in 47 patients, and 23 received systemic therapy due to medical recommendation (n=21) or patient choice (n=2). Among the 47 patients, 4 had no previous CRS (9%), 27 had at least a previous tertiary CRS (54%), and 24 had previous secondary and tertiary CRS (51%). There was no significant difference in median PFS4 between those who underwent quaternary CRS and those who did not (14.04 vs 12.48 months, respectively; HR, 0.74; 95% CI, 0.44–1.26; *P*=.27) (Figure 2, C; Table 2). There was a significant difference in median PFS4 based on residual disease status. Those who had no gross residual disease had the highest median PFS4, followed by those with residual disease ≤1 cm and residual disease >1 cm (18.84 vs 14.04 vs 3.96 months, respectively; *P*<.001).

Univariable analysis and Kaplan–Meier curves for OS are shown in Table 2 and Figure 2, D, respectively. On univariable

analyses, age <60 years (*P*=.02) and CRS at first progression (*P*<.001) were associated with significant improvement in survival. Targeted therapy at first progression was significantly associated with worse survival (*P*<.001). Of note, only 1 of 3 patients underwent any CRS (performed as first progression); her OS was 41.04 months, and she was still alive at the time of analysis. Despite having resectable disease and being eligible surgical candidates, the remaining 2 patients received systemic therapy only, and their OS was 16.56 and 30.84 months.

The median OS was significantly higher in those who underwent secondary CRS compared with those who did not undergo secondary CRS (181.92 vs 61.56 months, respectively; *P*=.002) (Figure 2, D). Although not statistically significant (*P*=.10), by residual disease status at secondary CRS, median OS was highest in those without gross residual disease (194.28 months), followed by those with residual disease ≤1 cm (155.88 months) and residual disease >1 cm (77.64 months).

TABLE 3
Multivariable analysis for progression-free survival after first recurrence and overall survival among patients with resectable disease

	PFS2			OS	
Characteristic	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (y)					
<60	97	Ref		Ref	
≥60	37	1.35 (0.89–2.03)	.16	2.25 (1.26–4.04)	.006
CRS					
No	7	Ref		Ref	
Yes	127	0.42 (0.19–0.92)	.03	0.28 (0.11–0.67)	.004
Chemotherapy					
No	53	Ref		Ref	
Yes	81	1.21 (0.81–1.82)	.35	1.49 (0.84–2.62)	.17
History of adjuvant therapy					
No	94	Ref		Ref	
Yes	40	1.17 (0.78–1.76)	.45	1.08 (0.60–1.94)	.81

CI, confidence interval; *CRS*, cytoreductive surgery; *HR*, hazard ratio; *OS*, overall survival; *PFS2*, progression-free survival after first recurrence; *Ref*, reference.

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Multivariable analyses performed for PFS2 and OS are shown in Table 3. When adjusting for age, adjuvant therapy, and chemotherapy, CRS at first progression was associated with significant improvement in PFS2 (HR, 0.42; 95% CI, 0.19–0.92; *P*=.03) and OS (HR, 0.28; 95% CI, 0.11–0.67; *P*=.004).

Locations of residual disease after CRS are shown in Supplemental Table 3. There were no predictive factors associated with achieving no gross residual disease following secondary CRS based on age (*P*=.13), previous chemotherapy (*P*=.20), number of metastatic sites (*P*=.84), or presence of upper abdominal disease (*P*=.24) on preoperative imaging.

Comment

Principal findings

Patients who underwent secondary CRS were observed to have a significant improvement in median PFS by 18.24 months, and the benefit of secondary CRS on PFS continued to be statistically significant when adjusting for confounders on multivariable analysis. Tertiary CRS was similarly found to be associated with a significant improvement in median PFS by 12.24 months. Although it was not statistically significant, quaternary CRS demonstrated a similar trend in improvement in PFS. The benefit of CRS on OS is quite striking given that those who underwent secondary CRS had a greater median OS benefit by 120.36 months. The benefit on OS remained statistically significant after controlling for confounders on multivariable analyses.

Results in the context of what is known

Multiple series have reported the feasibility of performing tumor cytoreduction for the management of recurrent aGCT.[14,15] Despite the feasibility of performing CRS in the recurrent setting, few studies have evaluated its associated clinical benefit, and most of the studies have had small sample sizes.[10] MITO-9 reported 33 of 35 patients with recurrent aGCT who underwent secondary CRS, and did not observe any difference in relapse rate by adding chemotherapy.[10] Other retrospective studies have reported improved outcomes of CRS in the recurrent setting, but do not account for selection bias (eg, poor performance status or considerable medical comorbidities) that precludes patients who likely have worse prognoses from surgical intervention, thus resulting in substantial confounders and limiting generalizability of study findings.[12,13]

Clinical implications

With a paucity of evidence delineating the role of surgical interventions in the management of aGCT in the recurrent setting, these study results support the role of secondary and tertiary CRS (when surgically feasible) in improving oncologic outcomes. There was a similar trend of improvement of PFS among patients who underwent quaternary CRS, but this was not statistically significant. The lack of observed association between quaternary CRS and PFS benefit could be attributed to several reasons. The first possibility is that the use of hormonal therapy may have a greater contribution to disease control compared with CRS at later lines of treatment (*P*=.01). Second, quaternary CRS may require stricter cytoreductive criteria for PFS benefit and may only be

beneficial in those with no gross residual disease (rather than optimal residual disease ≤1 cm). In addition, there were 20 of 47 patients who had quaternary CRS with unknown residual disease status; therefore, there may have been higher proportions of patients with suboptimal CRS (residual disease >1 cm) that may have contributed to a statistically insignificant result for median PFS4. Given that PFS and OS were observed to be inversely proportional to residual disease at the completion of secondary and quaternary CRS, this trend highlights the importance of achieving maximal cytoreduction; this follows a similar trend observed in epithelial ovarian cancer.[18] Thus, further evaluation of the role of quaternary CRS is indicated.

Research implications

Future collaborative studies are indicated to confirm the survival benefit of surgery and evaluate the role of quaternary CRS for recurrent aGCT. In our data, most patients underwent an open approach for cytoreduction. Therefore, future studies should examine the effect of minimally invasive tumor cytoreductive approaches on survival benefit. This study was not designed to determine predictive factors for achieving no gross residual disease during CRS in the recurrent setting; future studies are needed to establish selection criteria for ideal candidates for CRS.

Strengths and limitations

Given the rarity of aGCT, the establishment of a prospective, randomized controlled trial to evaluate the role of successive CRS in the recurrent setting will be extremely challenging, if not impossible. Thus, well-conducted retrospective studies are crucial to guide clinical management. One of the strengths of this study is that it is a large study that evaluates CRS in patients with aGCT in the recurrent setting. In addition, there is extensive follow-up with detailed information collected at each episode of disease progression to evaluate the contribution of CRS and other therapies to survival outcomes. However, this study has several limitations. Retrospective studies are subject to selection bias, which may consequently confound the effect of the studied intervention. Thus, at each progression, the study analyses were focused to only evaluate patients for whom tumor cytoreduction was feasible; therefore, patients with unresectable disease or who were poor surgical candidates because of comorbidities or performance status (upon clinical chart review) were excluded. Establishing criteria for eligible surgical patients was critical to minimizing bias and, relative to other published retrospective studies, may enable greater generalizability of the results to clinical practice. Another limitation includes temporal changes in management strategies or clinician preference of systemic therapies. Unfortunately, there have been few advances in the breadth of systemic agents for the management of recurrent aGCT over the decades. Furthermore, CRS continued to demonstrate a favorable association with survival (PFS and OS) after adjustment for chemotherapy and previous adjuvant therapy on multivariable analysis.

Conclusions

In this large cohort of patients with recurrent aGCT, when surgically feasible, CRS was associated with improvements in OS and in PFS at multiple, successive disease progressions for resectable disease. ■

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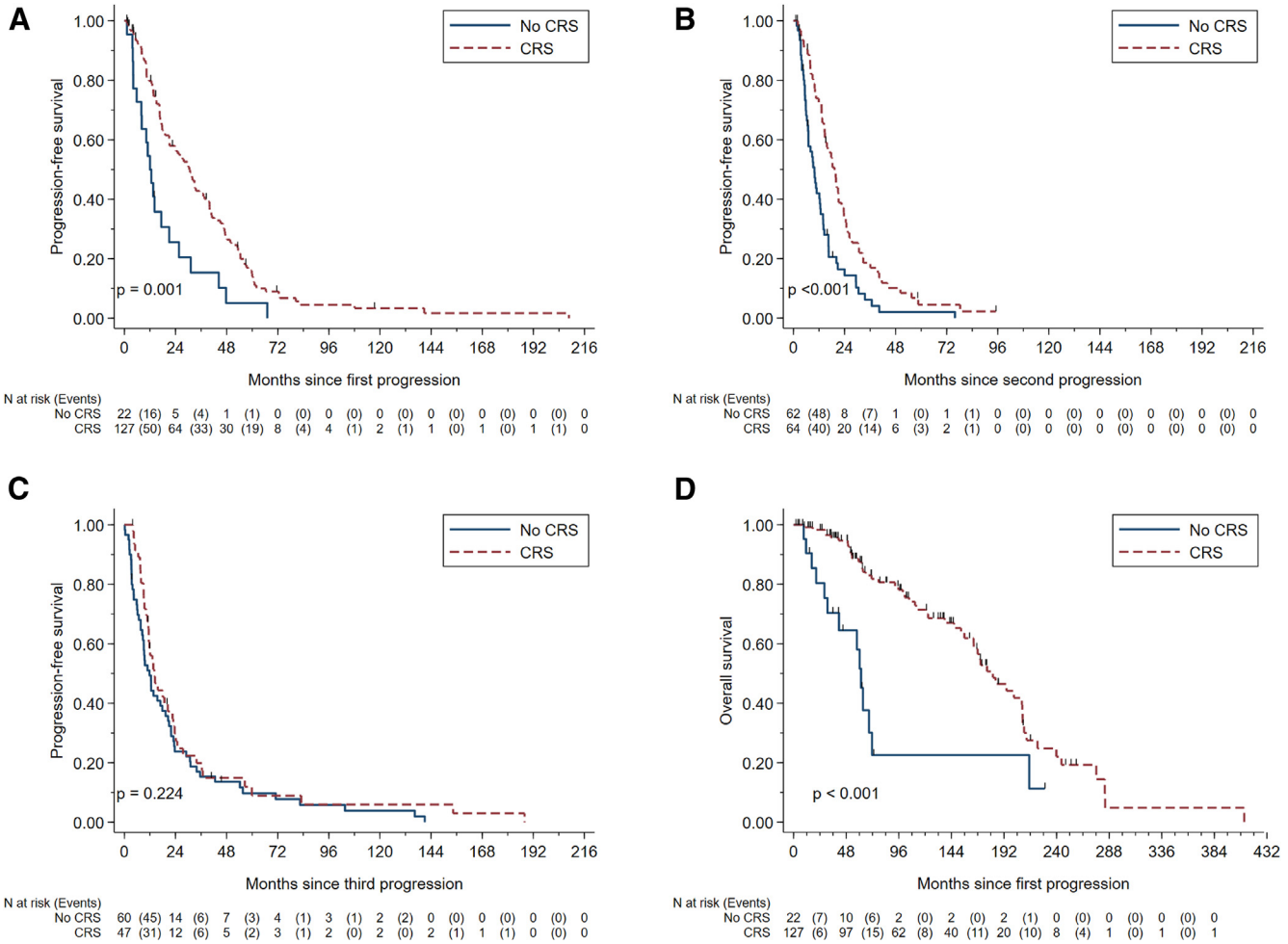
SUPPLEMENTAL FIGURE

Kaplan–Meier curves for PFS2, PFS3, PFS4, and OS among all patients



Kaplan–Meier survival curves for progression-free survival and OS for all patients. **A,** PFS2. **B,** PFS3. **C,** PFS4. **D,** OS.

CRS, cytoreductive surgery; *OS*, overall survival; *PFS2*, progression-free survival after first recurrence; *PFS3*, progression-free survival after second recurrence/progression; *PFS4*, progression-free survival after third recurrence/progression.

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SUPPLEMENTAL TABLE 1

Treatment modalities among patients with resectable disease at the first 3 disease progressions

Treatment modalities	First progression		Second progression		Third progression	
	CRS (n=127)	No CRS (n=7)	CRS (n=64)	No CRS (n=28)	CRS (n=47)	No CRS (n=23)
Chemotherapy/targeted therapy regimens						
Platinum with taxane doublet	45 (35)	3 (43)	16 (25)	5 (18)	7 (15)	1 (2)
Platinum with non-taxane doublet	6 (5)	0 (0)	2 (3)	0 (0)	0 (0)	1 (2)
BEP	17 (13)	0 (0)	4 (6)	1 (4)	0 (0)	0 (0)
Chemotherapy with bevacizumab	1 (1)	2 (3)	3 (5)	2 (7)	3 (6)	1 (2)
Other combination chemotherapy without bevacizumab	5 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Single-agent bevacizumab	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)
Single-agent chemotherapy	0 (0)	0 (0)	3 (5)	3 (11)	3 (6)	2 (4)
Other targeted therapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)
Hormonal therapy						
Aromatase inhibitor	17 (13)	1 (1)	9 (14)	9 (32)	11 (23)	6 (13)
Progesterone	1 (1)	0 (0)	2 (3)	1 (4)	4 (9)	1 (2)
SERM	3 (2)	0 (0)	6 (9)	3 (11)	6 (13)	1 (2)
GnRH agonist	11 (9)	2 (3)	6 (9)	5 (18)	6 (13)	9 (19)
Other	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)
None	37 (29)	0 (0)	26 (41)	0 (0)	14 (30)	0 (0)

Patients may have received chemotherapy/targeted therapy followed by hormonal therapy, and therefore percentages may not add up to 100%.

BEP, bleomycin, etoposide, cisplatin; *CRS*, cytoreductive surgery; *GnRH*, gonadotropin-releasing hormone; *SERM*, selective estrogen receptor modulator.

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SUPPLEMENTAL TABLE 2

Surgical characteristics among patients who underwent cytoreductive surgery

Characteristic	Secondary CRS (N=127) No. (%)	Tertiary CRS (N=64) No. (%)	Quaternary CRS (N=47) No. (%)
Surgical approach			
Laparotomy	98 (87)	53 (95)	39 (89)
Laparoscopic	10 (9)	3 (5)	2 (4)
Robotic	5 (4)	0 (0)	3 (7)
Unknown	14 (NA)	8 (NA)	3 (NA)
Procedures performed[a]			
Small/large bowel resection	18 (14)	10 (16)	9 (19)
Appendectomy	14 (7)	3 (5)	4 (9)
Pelvic lymphadenectomy	16 (13)	2 (3)	4 (9)
Para-aortic lymphadenectomy	9 (7)	0 (0)	4 (9)
Hepatic resection	1 (1)	4 (6)	5 (11)
Omentectomy	36 (28)	9 (14)	4 (9)
Splenectomy	5 (4)	2 (3)	1 (2)
Urinary procedures	9 (7)	5 (8)	4 (9)
Tumor resection	127 (100)	64 (100)	47 (100)
Residual disease			
R0	51 (68)	28 (72)	18 (67)
R≤1 cm	19 (25)	9 (23)	7 (26)
R>1 cm	5 (7)	2 (5)	2 (7)
Unknown	52 (NA)	25 (NA)	20 (NA)

CRS, cytoreductive surgery; *NA*, not applicable; *R0*, no gross residual disease present at end of cytoreduction; *R≤1*, gross residual disease ≤1 cm present at end of cytoreduction; *R>1 cm*, gross residual disease >1 cm present at end of cytoreduction.

[a] Percentages may not add up to 100%.

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SUPPLEMENTAL TABLE 3
Locations of residual disease among patients who underwent cytoreductive surgery

Locations of residual disease after secondary CRS
Perihepatic/hepatic
Cul-de-sac
Para-aortic
Small/large bowel mesentery
Locations of residual disease after tertiary CRS
Liver
Small/large bowel
Miliary disease
Locations of residual disease after quaternary CRS
Large bowel
Miliary disease

CRS, cytoreductive surgery.
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