



Research Report

Quaternary and beyond cytoreduction: An updated and expanded analysis



Beryl L. Manning-Geist^a, Dennis S. Chi^{a,b}, Kara Long Roche^{a,b}, Oliver Zivanovic^{a,b}, Yukio Sonoda^{a,b}, Ginger J. Gardner^{a,b}, Roisin E. O’Cearbhaill^{c,d}, Nadeem R. Abu-Rustum^{a,b}, Mario M. Leitao Jr.^{a,b,*}

^a Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^b Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, United States

^c Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^d Department of Medicine, Weill Cornell Medical College, New York, NY, United States

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ABSTRACT

Objective: We sought to describe the clinicopathologic features and outcomes of patients undergoing quaternary, quinary, or senary cytoreductive surgery for ovarian cancer.

Methods: We retrospectively identified patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who underwent quaternary or beyond cytoreduction at our institution between 1/1/1989 and 12/31/2020. Kaplan-Meier curves were used to estimate survival and compared using the log-rank test. Cox-proportional hazards regression was used to detect variables associated with survival.

Results: Twenty patients underwent 24 quaternary (n = 20), quinary (n = 3), or senary (n = 1) cytoreductive surgeries. Most patients had high-grade (89.5%) and serous (75.0%) tumors. At the time of quaternary cytoreduction, 44.7% of patients had single-site disease and 85.0% achieved a complete gross resection. After quaternary cytoreduction, 34.8% of patients developed a surgical complication, most of which were grade 1 or 2. Postoperatively, 80.0% of patients received additional medical treatment and 20.0% underwent observation alone. On univariate analysis, factors associated with progression-free survival included prolonged treatment-free interval (TFI), platinum sensitivity, and complete gross resection. Factors associated with disease-specific survival included platinum sensitivity and complete gross resection. Quinary and senary surgeries were associated with similar safety profiles, with no surgical complications reported. After quinary surgery, progression-free survival ranged from 5.0 to 216.0 months.

Conclusions: In carefully selected patients, quaternary cytoreduction may be associated with acceptable morbidity and a relatively robust disease-specific survival. Patients who present to surgery with a prolonged TFI and achieve a complete gross resection likely derive the greatest benefit from quaternary surgery.

1. Introduction

Improvements in ovarian cancer treatment have led to a growing number of long-term survivors. In 1990, the 5-year survival rates for women with stage III and IV ovarian cancer were 45–53% and 18–20%, respectively (Silverberg et al., 1990). In 2021, these rates have improved to 64–76% and 30%, respectively (Siegel et al., 2021). A study of >11,000 patients with epithelial ovarian cancer diagnosed between 1994 and 2001 reported 10-year survival rate of 31% (Cress et al., 2015).

Treatment for recurrent ovarian cancer usually necessitates multiple

lines of systemic therapy. Additional cytoreductive surgery may benefit a select group of patients in the recurrent setting, although the practice is controversial (Coleman et al., 2019; Du Bois et al., 2017; Shi et al., 2021). Our group, among others, has published on outcomes in carefully selected patients who underwent secondary or tertiary cytoreduction (Manning-Geist et al., 2021; Chi et al., 2006). In patients presenting with recurrence after tertiary cytoreduction, the data for further surgery are sparse. Specifically, there have been three small retrospective studies published on patients who underwent quaternary surgery for recurrent ovarian cancer. One of these studies, which was from our group, reported on 15 patients who underwent quaternary surgery with

* Corresponding author at: Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States.

E-mail address: leitao@mskcc.org (M.M. Leitao).

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cytoreductive intent (Shih et al., 2010). Fotopoulou et al. reported on a cohort of 49 patients who underwent quaternary surgery with cytoreductive and/or palliative intent (Fotopoulou et al., 2013). Finally, Bacalbasa et al. reported on 20 patients who underwent quaternary surgery with cytoreductive and/or palliative intent (Bacalbasa et al., 2015). To some degree, all 3 studies demonstrated the safety and efficacy of quaternary cytoreduction; however, the survival outcomes after quaternary surgery are difficult to compare across these studies due to differences in inclusion criteria and rates of complete cytoreduction.

This study is an updated and expanded cohort of patients with epithelial ovarian cancer who underwent quaternary, quinary, or senary cytoreductive surgery at our institution. Our goal was to inform patient selection and counseling in this setting of ovarian cancer recurrence.

2. Methods

After Institutional Review Board approval, patients who underwent quaternary surgery for epithelial ovarian, peritoneal, or fallopian tube cancer with cytoreductive intent at our institution between 1/1/1989 and 12/31/2020 were identified from a previously curated database of 114 tertiary cytoreductions. Exclusion criteria included the following: having undergone quaternary surgery for reasons other than cytoreduction, such as for correction of malignant bowel obstruction; non-epithelioid histology; or having undergone secondary or tertiary surgery as a second-look laparoscopy or laparotomy unprompted by evidence of recurrent disease on exam or imaging.

Variables of interest were abstracted from the electronic medical records. Stage at initial diagnosis was assigned based on the International Federation of Gynecology and Obstetrics (FIGO) 2014 staging system. Preoperative CA-125 values were obtained from preoperative laboratory testing performed within 1 month of surgery. The number of sites of tumor recurrence and volume of residual disease were classified based on descriptions from operative reports. Optimal cytoreduction was defined as maximal residual tumor volume ≤ 1 cm for initial cytoreduction based on Gynecologic Oncology Group (GOG) definitions from trials completed during this study period (Omura et al., 1989; Ozols et al., 2003; Walker et al., 2006). Complete gross resection (CGR) was defined as resection of all macroscopic residual disease and was documented for secondary and beyond surgeries to reflect evolving surgical objectives (Eisenkop et al., 2006). Platinum sensitivity was reported at the time of quaternary cytoreduction. Platinum resistance was defined as progression while on platinum therapy and/or progression or recurrence within 6 months of completion of last platinum therapy; these criteria are consistent with generally accepted definitions, which were not used in our group's previous publication on quaternary cytoreduction (Shih et al., 2010; Pfisterer and Ledermann, 2006). After quaternary cytoreduction, postoperative therapies were defined as those given immediately following surgery, including cytotoxic therapies and hormonal manipulation. Postoperative complications that occurred within 30 days of surgery were noted and graded using a previously validated institutional grading system (Strong et al., 2015). Grade 1 complications were those that only required the use of oral medications or bedside interventions. Grade 2 complications were those that required intravenous medications, total parenteral nutrition, enteral nutrition, or a blood transfusion. Grade 3 complications were those that required interventional radiology, therapeutic endoscopy, intubation, angiography, or surgery. Grade 4 complications were those that resulted in residual and lasting disability requiring major rehabilitation or organ resection. Grade 5 complications were those that resulted in death.

Survival analyses included progression-free survival (PFS), defined as the number of months between the date of quaternary cytoreduction and either disease progression or death from disease. Disease-specific survival (DSS) was defined as the number of months between the date of quaternary cytoreduction and death from disease. Patients who experienced death due to reasons not attributable to cancer were censored for follow-up at date of death. Patients alive and disease-free or

alive with disease were censored for PFS and DSS, respectively, at date of last follow-up. Survival curves were estimated using the Kaplan-Meier method, and p values were generated using log-rank tests. Associations were shown as hazard ratios (HRs) with 95% confidence intervals (95% CIs). All statistical analyses were performed using SPSS version 26.0 (Armonk, NY).

3. Results

3.1. Patient population and operative characteristics

Among the 20 patients included in the analysis, there were 24 surgeries (20 quaternary, 3 quinary, and 1 senary cytoreduction). The majority (75.0%) of patients had serous histologies. In total, 2 patients had low-grade disease—one with grade 1 serous carcinoma and one with grade 1 mucinous adenocarcinoma. Of 8 patients with available genetic testing, 2 (25.0%) harbored a germline *BRCA* mutation. Most patients underwent optimal cytoreduction at the time of primary surgery (76.9%) and achieved a CGR at the time of secondary and tertiary cytoreduction (72.2% and 90.0%, respectively). Baseline patient characteristics are included in Table 1.

Of the 20 patients who underwent quaternary surgery, median patient age was 61.1 years (range, 46.0–72.7 years). Clinicopathologic characteristics at the time of quaternary cytoreduction are reported in Table 1. The median treatment-free interval (TFI) prior to quaternary cytoreduction was 14.1 months (range, 0.9–135.0 months). Patients received a median of 3 lines of chemotherapy (range, 2–9 lines) prior to quaternary surgery. All patients were platinum-sensitive following upfront therapy, and 70.0% had platinum-sensitive disease prior to quaternary surgery. Of the 20 patients who underwent quaternary surgery, 18 had available preoperative imaging. Of these 18 patients, 15 (83.3%) had a computed tomography (CT) scan, 1 (5.6%) had magnetic resonance imaging (MRI), and 2 (11.1%) had a positron emission tomography (PET)-CT. On imaging, 13 (72.2%) of 18 patients had single-site disease.

At the time of quaternary cytoreduction, 44.7% of patients had a single site of recurrent disease, and 85.0% achieved a CGR. After surgery, 13 patients (65.0%) received cytotoxic chemotherapy, 4 (20.0%) were observed, 2 (10.0%) received hormonal manipulation, and 1 (5.0%) received a poly (ADP-ribose) polymerase (PARP) inhibitor. Cytotoxic regimens were single-agent non-platinum-based ($n = 5$), single-agent platinum-based ($n = 1$), platinum doublets ($n = 6$), and non-platinum doublets ($n = 1$) (Supplementary Table 1). Among the 13 patients who received cytotoxic chemotherapy, 3 (23.1%) also underwent bevacizumab maintenance. Median time to initiation of postoperative chemotherapy following quaternary cytoreduction was 6.6 weeks (range, 4.6–20.2 weeks); one patient experienced a prolonged delay due to a postoperative abscess. Among the 4 patients who underwent observation, median time to additional therapy was 9.6 months (range, 6.3–25.5 months).

Median patient age at quinary surgery was 66.0 years. The patient undergoing senary surgery was 66 years old. Of patients undergoing quinary ($n = 3$) and senary surgery ($n = 1$), one patient had high-grade serous adenocarcinoma, one had low-grade mucinous adenocarcinoma, and one had endometrioid adenocarcinoma of unknown grade (this patient underwent quinary and senary cytoreduction). *BRCA* status was not available for these patients. All patients had 1–2 sites of disease at the time of quinary or senary surgery. Two of 4 surgeries resulted in a CGR. After quinary surgery, the patient with low-grade mucinous adenocarcinoma had not recurred at 216.0 months of follow-up. The patient with high-grade serous adenocarcinoma underwent observation for 9.3 months before starting additional cytotoxic therapy. The patient with endometrioid adenocarcinoma received postoperative hormonal therapy with tamoxifen. This patient subsequently recurred 5.0 months later and underwent senary surgery followed by postoperative radiation.

Of the 24 total surgeries, 91.7% were performed by our gynecology

Table 1
Clinicopathologic characteristics*.

| Characteristic | n (%) |
|--|---------------------|
| Age at initial diagnosis, years | |
| Median (range) | 51.4 (38.1–66.0) |
| Origin of disease | |
| Fallopian tube | 2 (10.0%) |
| Ovary | 18 (90.0%) |
| Stage at diagnosis | |
| I | 1 (5.3%) |
| II | 4 (21.0%) |
| III | 13 (68.4%) |
| IV | 1 (5.3%) |
| Grade | |
| Low | 2 (10.5%) |
| High | 17 (89.5%) |
| Histology | |
| Serous | 15 (75.0%) |
| Endometrioid | 2 (10.0%) |
| Mucinous | 2 (10.0%) |
| Mixed | 1 (5.0%) |
| BRCA | |
| Wild type | 6 (75.0%) |
| Mutated | 2 (25.0%) |
| Initial cytoreduction | |
| Optimal | 10 (76.9%) |
| Suboptimal | 3 (23.1.0%) |
| Time to first recurrence, months | |
| Median (range) | 23.0 (10.7–326.6) |
| Secondary cytoreduction | |
| Complete gross resection | 13 (72.2%) |
| Any residual | 5 (27.8%) |
| Time to second recurrence, months | |
| Median (range) | 22.7 (10.8–94.1) |
| Tertiary cytoreduction | |
| Complete gross resection | 18 (90.0%) |
| Any residual | 2 (10.0%) |
| Time to third recurrence, months | |
| Median (range) | 17.3 (2.0–132.1) |
| Age at quaternary cytoreduction, years | |
| Median (range) | 61.1 (46.0–72.7) |
| BMI at quaternary cytoreduction, kg/m ² | |
| Median (range) | 27.8 (20.5–40.6) |
| TFI prior to quaternary cytoreduction, months | |
| Median (range) | 14.1 (0.9–135.0) |
| Platinum sensitivity at the time of quaternary cytoreduction | |
| Sensitive | 14 (70.0%) |
| Resistant | 6 (30.0%) |
| CA-125 at quaternary cytoreduction, U/mL | |
| Median (range) | 26 (5–2336) |
| Residual disease | |
| Complete gross resection | 17 (85.0%) |
| Residual disease | 2 (10.0%) |
| Unknown | 1 (5.0%) |
| Sites of recurrence | |
| Single | 12 (44.7%) |
| Multiple | 7 (55.3%) |
| Size of recurrence, cm | |
| Median (range) | 4 (0.5–21.0) |
| Surgical procedure performed (n = 24) | |
| Abdominopelvic mass resection | 10 (41.7%) |
| Large bowel resection | 6 (25.0%) |
| Small bowel resection | 2 (8.3%) |
| Partial liver resection | 4 (16.7%) |
| Paraortic lymph node resection (open) | 3 (12.5%) |
| Pelvic lymph node resection (open) | 1 (4.2%) |
| | 1 (4.2%) |

Table 1 (continued)

| Characteristic | n (%) |
|---|-----------------------------------|
| | Pelvic lymph node resection (MIS) |
| | Diaphragm resection |
| | Lung resection |
| | Posterior exenteration |
| Adjuvant therapy after quaternary cytoreduction | |
| | Cytotoxic |
| | Hormonal |
| | Observation |
| | PARP inhibitor |

Patients with unavailable data include: stage at diagnosis (n = 1), grade (n = 1), BRCA status (n = 12), residual disease at primary cytoreduction (n = 7), residual disease at secondary cytoreduction (n = 2), sites of recurrence (n = 1)

TFI, treatment-free interval; MIS, minimally invasive surgery; PARP, poly (ADP-ribose) polymerase

* N = 20 patients with 24 cytoreductions

service. The surgeries performed are detailed in Table 1. Following surgery, the median length of stay for all patients was 6 days (range, 1–18 days). Approximately 34.8% of patients developed a postoperative complication, including three grade 1, three grade 2, one grade 3, and one grade 4 complication. The grade 3 complication was a pelvic abscess requiring drainage by interventional radiology. The grade 4 complication was postoperative respiratory insufficiency requiring intensive care unit admission. The most common complications were pelvic abscess requiring antibiotics (n = 2), postoperative small bowel obstruction or ileus (n = 2), and wound infection (n = 2). There were no postoperative deaths.

3.2. Progression-free survival

PFS was calculated for the 20 patients who underwent quaternary cytoreduction. Sixteen patients (80.0%) recurred. Median follow-up was 20.0 months (range, 0.8–224.0 months). Among the patients who recurred, median time to recurrence after quaternary cytoreduction was 6.6 months (range, 0.8–58.4 months).

Various clinicopathologic features were examined for association with PFS (Table 2). TFI prior to quaternary cytoreduction, platinum sensitivity, and residual disease after quaternary cytoreduction were significantly associated with prolonged PFS. Of note, a TFI ≥ 6 months prior to quaternary cytoreduction was associated with a 21-month improvement in median PFS when compared to a TFI < 6 months (HR 0.12; 95% CI: 0.03–0.42; Fig. 1). In a multivariable model, both TFI and platinum sensitivity maintained significance (Table 2).

3.3. Disease-specific survival

DSS was calculated for the 20 patients who underwent quaternary cytoreduction. Ten patients (50.0%) ultimately died of disease. Among those who died of disease, median time to death after quaternary cytoreduction was 23.1 months (range, 9.5–120.0 months).

The associations between clinicopathologic features and DSS are reported in Table 3. Platinum sensitivity and residual disease at quaternary cytoreduction were significantly associated with improved DSS (Fig. 2). CGR was associated with a 39.4-month DSS, compared with 9.5 months when any residual disease was left. Of note, a TFI ≥ 6 months prior to quaternary cytoreduction was associated with a >100-month improvement in median DSS when compared to a TFI < 6 months (HR 0.004; 95% CI: 0.00–5.52; Fig. 3). When combined into a multivariable model, only platinum sensitivity maintained significance (Table 3).

4. Discussion

Here, we describe a cohort of 20 patients who underwent quaternary, quinary, or senary cytoreduction. In all cases, surgical intent was for

Table 2
Factors associated with progression-free survival.

| Variable | n | Median PFS (mo) | Univariate HR (95% CI) | Univariate p value | Multivariate HR (95% CI) | Multivariate p value |
|--|----|-----------------|------------------------|--------------------|--------------------------|----------------------|
| Age at quaternary surgery | | | | | | |
| <60 years | 8 | 4.4 | ref | | | |
| ≥60 years | 12 | 12.5 | 0.34 (0.11–1.05) | 0.06 | | |
| Histology | | | | | | |
| Non-serous | 5 | 6.6 | ref | | | |
| Serous | 15 | 6.6 | 0.69 (0.22–2.23) | 0.79 | | |
| Tertiary cytoreduction | | | | | | |
| CGR | 18 | 6.6 | ref | | | |
| Any residual | 2 | 4.4 | 1.2 (0.26–5.48) | 0.83 | | |
| Time from tertiary to quaternary cytoreduction | | | | | | |
| ≤2 years | 11 | 6.1 | ref | | | |
| >2 years | 9 | 7.7 | 0.51 (0.17–1.50) | 0.22 | | |
| TFI prior to quaternary cytoreduction | | | | | | |
| <6 months | 8 | 3.9 | ref | | | |
| ≥6 months | 12 | 25.0 | 0.12 (0.03–0.42) | 0.001* | 0.01 (0.00–0.19) | <0.01* |
| Platinum sensitivity | | | | | | |
| Sensitive | 14 | 12.5 | ref | | | |
| Resistant | 6 | 4.4 | 4.3 (1.34–14.00) | <0.02* | 15.0 (1.1–211.1) | <0.05* |
| Quaternary cytoreduction | | | | | | |
| CGR | 17 | 6.6 | ref | | | |
| Any residual | 2 | 1.1 | 6.3 (1.03–38.14) | <0.05* | 7.32 (0.62–86.7) | 0.11 |
| Sites of recurrence | | | | | | |
| Single | 12 | 6.6 | ref | | | |
| Multiple | 7 | 7.7 | 0.56 (0.17–1.81) | 0.33 | | |
| Yes | 13 | 6.7 | ref | | | |
| No | 4 | 6.1 | 0.81 (0.38–3.58) | 0.80 | | |

Postoperative chemotherapy

PFS, progression-free survival; CGR, complete gross resection; TFI, treatment-free interval

*statistically significant

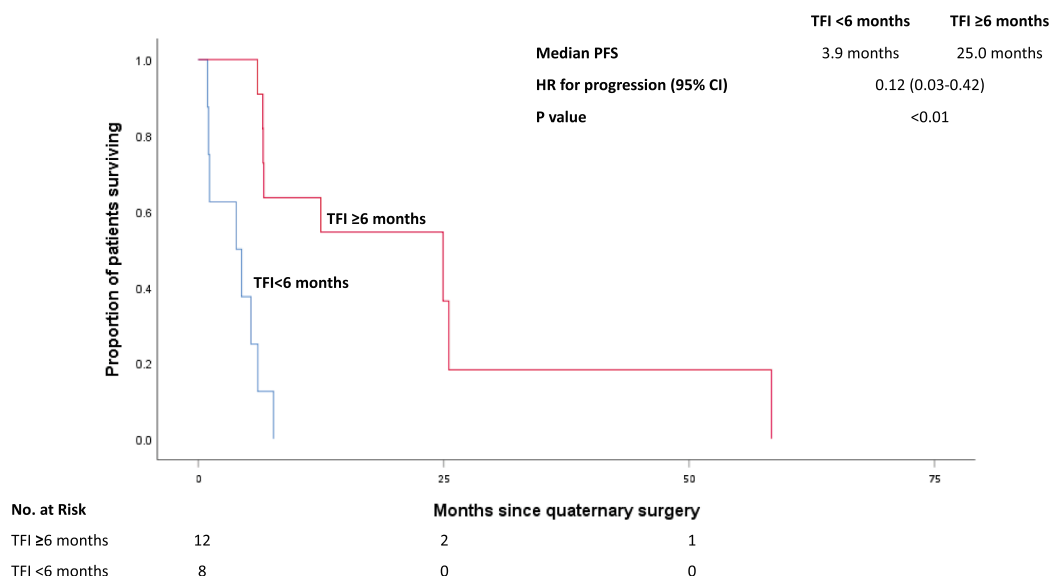


Fig. 1. Association between treatment-free interval (TFI) prior to quaternary cytoreduction and progression-free survival (PFS).

cytoreduction, and it should be noted that this cohort was already highly selected, and likely to achieve complete gross resection. For example, the majority of patients were > 5 years past the date of their initial diagnosis, and the median TFI prior to quaternary cytoreduction was 14.1 months. Furthermore, patients offered quaternary cytoreduction were those most likely to undergo a complete cytoreductive effort, as 72% had single-site disease on preoperative imaging and 85% had no gross residual disease after quaternary surgery.

Demographic and pathologic features, such as patient age at

quaternary cytoreduction or tumor grade/histology were not associated with oncologic outcome. Variables significantly associated with PFS on univariate analysis were TFI (≥6 months vs. < 6 months), platinum sensitivity, and volume of residual disease after quaternary cytoreduction (CGR vs. residual disease). TFI and platinum sensitivity were also significantly associated with DSS on univariate analysis. In many ways, our findings reinforce those of other studies in ovarian cancer that established residual tumor volume following cytoreductive surgery as a strong prognostic factor (Manning-Geist et al., 2021 May 25; Chi et al.,

Table 3
Factors associated with disease-specific survival.

| Variable | n | Median DSS (mo) | Univariate HR (95% CI) | Univariate p value | Multivariate HR (95% CI) | Multivariate p value |
|--|----|-----------------|------------------------|--------------------|--------------------------|----------------------|
| Age at quaternary surgery | | | | | | |
| <60 years | 8 | 19.0 | ref | | | |
| ≥60 years | 12 | 86.4 | 0.38 (0.10–1.35) | 0.13 | | |
| Histology | | | | | | |
| Non-serous | 5 | 39.4 | ref | | | |
| Serous | 15 | 33.7 | 1.93 (0.40–9.43) | 0.42 | | |
| Tertiary cytoreduction | | | | | | |
| CGR | 18 | 39.4 | ref | | | |
| Any residual | 2 | 19.0 | 1.07 (0.13–8.77) | 0.95 | | |
| Time from tertiary to quaternary cytoreduction | | | | | | |
| ≤2 years | 11 | 25.2 | ref | | | |
| >2 years | 9 | 86.4 | 0.40 (0.09–1.91) | 0.25 | | |
| TFI prior to quaternary cytoreduction | | | | | | |
| <6 months | 8 | 19.0 | ref | | | |
| ≥6 months | 12 | 120.0 | 0.004 (0.00–5.52) | 0.14 | | |
| Platinum sensitivity | | | | | | |
| Sensitive | 14 | 86.4 | ref | | | |
| Resistant | 6 | 19.0 | 17.42 (1.96–155.11) | 0.01* | 12.1 (1.2–119.6) | <0.04* |
| Quaternary cytoreduction | | | | | | |
| CGR | 17 | 39.4 | ref | | | |
| Any residual | 2 | 9.5 | 10.84 (1.50–78.30) | <0.02* | 3.3 (0.43–25.3) | 0.25 |
| Sites of recurrence | | | | | | |
| Single | 12 | 39.4 | ref | | | |
| Multiple | 7 | 19.0 | 1.77 (0.43–7.38) | 0.43 | | |
| Postoperative chemotherapy | | | | | | |
| Yes | 13 | 25.2 | ref | | | |
| No | 4 | 120.0 | 0.20 (0.02–1.72) | 0.1 | | |

DSS, disease-specific survival; CGR, complete gross resection; TFI, treatment-free interval
* statistically significant

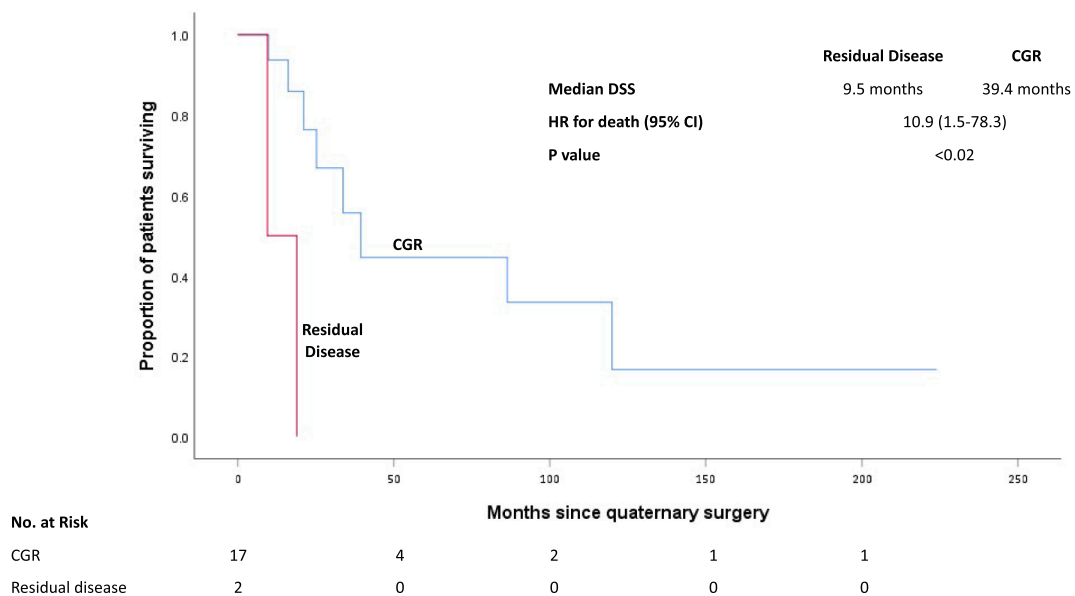


Fig. 2. Association between residual disease status at quaternary cytoreduction and disease-specific survival (DSS). CGR, complete gross resection.

2006; Manning-Geist et al., 2018; Fotopoulou et al., 2013). In secondary cytoreduction, three large randomized controlled trials have investigated whether surgery may benefit patients with recurrent ovarian cancer, with conflicting results (Coleman et al., 2019; Shi et al., 2021; Du Bois et al., 2020). Although these studies employed different selection criteria, each study selected patients thought to have resectable disease. Although survival data between trials are not directly comparable due to differing selection criteria, in DESKTOP III, complete gross resection compared to incomplete resection was associated with

significantly longer median overall survival (60.7 months versus 28.8 months, respectively) (Du Bois et al., 2020). In tertiary cytoreduction, randomized data are not available. However, retrospective data from our group reported a 60.3-month DSS for patients who achieved a CGR compared with 27.5 months for those left with any residual macroscopic disease (Manning-Geist et al., 2021). In quaternary surgery, Fotopoulou et al. reported a 43-month overall survival for patients who achieved a CGR compared with 13.4 months for those left with any residual disease (Fotopoulou et al., 2013). In our cohort, CGR was associated with a 39.4-

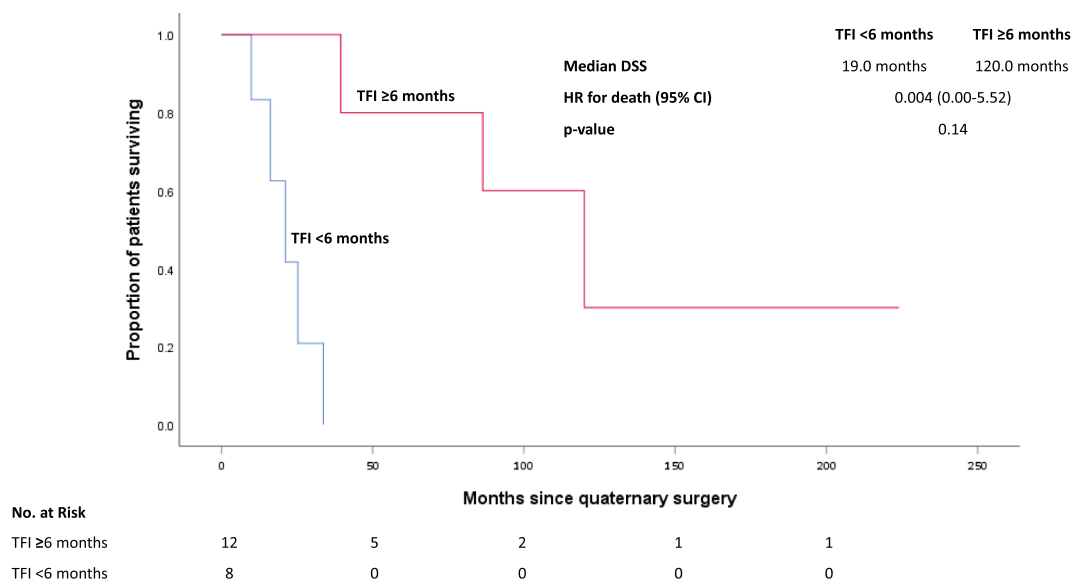


Fig. 3. Association between treatment-free interval (TFI) prior to quaternary cytoreduction and disease-specific survival (DSS).

month DSS, compared with 9.5 months when any residual disease was left. Our findings, along with the existing data in the cumulative body of cytoreductive literature, suggest that select patients who are likely to achieve a CGR should be considered for quaternary cytoreduction.

Certain treatment-related factors, including TFI and platinum sensitivity, were also associated with survival outcomes. These variables may help providers select patients most likely to benefit from quaternary cytoreduction. In our study, there was a 22-month longer median PFS and 101-month longer DSS for patients with a TFI ≥ 6 months compared to those with a TFI < 6 months. The association of increased TFI has been recognized in secondary and tertiary cytoreduction (Manning-Geist et al., 2021; Chi et al., 2006). This is the first study, to our knowledge, to associate increased TFI with improved survival outcomes in the quaternary setting. Given our findings, TFI should be considered when selecting patients for quaternary cytoreduction. With regards to platinum sensitivity, platinum-sensitive disease was significantly associated with PFS and DSS on univariate and multivariate analyses. All randomized trials on secondary cytoreduction have included patients with platinum-sensitive disease, reflecting the consensus that patients with chemosensitive disease benefit most from higher-order cytoreduction (Coleman et al., 2019; Du Bois et al., 2017; Shi et al., 2021). Retrospective data on recurrent ovarian cancer have also reported improved survival associated with platinum-sensitive disease following tertiary cytoreduction (Manning-Geist et al., 2021). Our findings suggest a similar survival benefit with quaternary surgery in the platinum-sensitive patient population.

Among the 24 surgeries performed, postoperative complications occurred in 35% of cases. However, only 2 patients (8.3%) experienced a grade 3 or 4 postoperative complication, which parallels grade 3 complication rates of 4–16% reported in primary, interval, secondary, and tertiary surgery at our institution (Manning-Geist et al., 2021; Chi et al., 2006; Mueller et al., 2016).

Of the 20 patients who underwent quaternary surgery, 65% received postoperative chemotherapy and 15% received hormonal therapy or PARP inhibition. There were no observed differences in PFS or DSS between patients who received additional cytotoxic therapy compared to those who underwent observation, although analysis was limited by the sample size (n = 4 patients undergoing observation). This finding differs from the study on quaternary cytoreduction by Fotopoulou et al., in which the authors reported significantly worse overall survival for patients who did not receive postoperative chemotherapy (Fotopoulou et al., 2013). The patient population in the Fotopoulou study differed

from our patient population in important ways. Unlike the Fotopoulou study, our surgical intent was cytoreduction and did not include palliative surgeries. Also, our CGR rate was 85%, compared to 32.6% in the Fotopoulou study. Finally, Fotopoulou et al. reported that 14.2% of their patients were too weak to receive chemotherapy and that 2% of their patients (n = 1) experienced postoperative mortality. In our study, none of the patients were deemed too frail to receive chemotherapy, and there were no postoperative deaths. Further investigation on the benefit of postoperative chemotherapy following CGR of recurrent disease in the quaternary surgical setting is warranted.

Our analyses are limited by the retrospective nature of our study and the non-randomized decision to pursue quaternary and beyond cytoreduction. Our study includes patients treated at a single institution, although the surgeons who performed these surgeries have varied over the years. Our study is further limited by the evolution of ovarian cancer management that overlapped the timeframe of our study (1989–2020), which included adapted definitions of optimal cytoreduction, advancements in radiographic imaging, and innovation in therapeutic options for recurrent ovarian cancer (Eisenhauer, 2017). Finally, this study is limited by the small patient population. Here, we have expanded on the cohort included in our prior publication, which allowed for more robust statistical comparisons (Shih et al., 2010). As before, we report improved survival associated with complete gross resection. However, we did not find number of recurrence sites (single versus multiple) to be significantly associated with survival; patients with single-site disease had a median DSS of 39.4 months compared to 19.0 months in patients with multiple-site disease. It is possible that this survival difference may be significant in a larger cohort, as patients with single-site disease are more likely to undergo complete gross resection compared to patients with multiple-site disease.

As medical treatment for recurrent ovarian cancer advances, surgical practice must also be refined. Appropriate integration of minimally invasive surgery, thoughtful triage of patients to primary versus interval debulking, and the use of higher order cytoreduction (secondary and beyond) are just a few examples of how surgery can be individualized. When deciding whether to pursue surgery in the recurrent setting, surgeons must integrate clinical intuition with the available data. Our study demonstrated acceptable morbidity with quaternary cytoreduction and a relatively robust DSS for patients who achieved a CGR.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2021.100851>.

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