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Efforts at maximal cytoreduction improve survival in ovarian cancer patients, even when complete gross resection is not feasible☆

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HIGHLIGHTS

- This study confirms the strong association between survival and RD0 after PDS in advanced OC.
- Our data shows benefits of improved surgical cytoreduction through practice change.
- When resection to minimal RD is likely, PDS followed by chemotherapy is preferred treatment for OC.

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ABSTRACT

Objective. We sought to determine survival associated with residual disease (RD) after primary debulking surgery (PDS) for advanced ovarian cancer (OC), and evaluate impact on complications and survival after practice changes to improve PDS.

Methods. Outcome variables were collected for patients undergoing PDS for FIGO (2009) stage IIIC OC from 2003 to 2011. The cohort was divided into time periods (2003–2006 vs. 2007–2011), before and after cytoreduction standardization. RD categories were: RD0, RD 0.1–0.5 cm, RD 0.6–1.0 cm, and RD > 1 cm. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method.

Results. 447 patients (mean age, 65.3 years) met inclusion criteria. RD for the entire cohort: RD0 = 44.5%; RD 0.1–0.5 cm = 30.9%; RD 0.6–1.0 cm = 11.4%; and RD > 1 cm = 13.2%, with median OS of 58 months, 35 months, 29 months, and 22 months, respectively. OS was significantly better for RD0 vs. all other RD categories ($p \le 0.001$), and for RD 0.1–1.0 cm vs. RD > 1 cm ($p = 0.01$). RD0 improved from 32.7% to 54.3% ($p < 0.001$), and RD > 1 cm decreased from 20.3% to 7.3% ($p < 0.001$) when comparing the 2003–2006 ($n = 202$) vs. 2007–2011 ($n = 245$) cohorts. Surgical complexity increased in the latter time period (24.3% vs. 41.2%). 30-day Accordion grade 3–4 morbidity remained consistent (18.8% vs. 20.8%, $p = 0.60$), 30-day mortality decreased (4.5% to 1.2%, $p = 0.035$), and median OS improved from 36 to 40 months after cytoreduction standardization.

Conclusion. Patients with RD0 had longest OS, with survival advantage for RD1 when compared to RD > 1 cm. These data support PDS to lowest RD even when RD0 cannot be obtained. Practice improvement efforts can increase RD0 rates, improving OS without compromising morbidity.

1. Introduction

For more than four decades, primary debulking surgery (PDS) has been a principle component in the treatment of ovarian carcinoma (OC) [1,2]. Survival is strongly correlated with lower residual disease (RD) [3–5]. Prior studies have shown that, while cytoreduction to <1 cm RD (RD1) provides survival benefit, no gross residual disease (referred to as RD0 for the present study) is associated with longer overall survival (OS) [4,6]. As a result, recent efforts regarding surgical management of OC has evolved to an ever-increasing focus on RD0 as the primary surgical goal.

High complexity surgery has been shown to be necessary to achieve maximal cytoreduction in most cases of advanced OC [3,7,8]. The vast literature on outcomes for advanced OC has contributed to the routine use in some centers, of splenectomy, diaphragm resection, celiac nodal resection, and/or multiple bowel resections to achieve lower RD

☆ All authors contributed to the concept and design of this study, in addition to the drafting and editing of the manuscript.

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[9–12]. Correspondingly, rates of resection to RD0 and RD1 have improved [3,6]. Analysis of our own practice in 2006 identified specific surgical practices associated with lowest residual disease and longest survival [3]. We also observed that despite a high rate of successful resection, there were significant variations in practice patterns across our division. As a result of those studies, we initiated measures to standardize surgical management, reduce morbidity and reduce residual disease [13].

Concomitant with the heightened awareness of the association between RD0 and survival, several scoring systems and algorithms have been proposed to predict surgical outcome at primary debulking surgery [14–16]. With the heightened emphasis on RD0, many centers have suggested that use of these triage systems can direct patients to neoadjuvant chemotherapy (NACT) instead of primary debulking surgery in cases where RD0 is unlikely. This is potentially problematic as most triage systems are relatively non-specific, have not been validated in settings with high rates of surgical resection, and may dismiss the value of RD1 resections.

While recognizing the survival advantage from complete cytoreduction, we are concerned that the benefit of resection to small volume residual disease is being minimized. We hypothesize that there is a clinically relevant spectrum in survival benefit for progressively lower RD, even when maximal surgical efforts are unable to achieve RD0. In the present study we sought to describe the relative survival benefits of no gross RD and minimal gross residual disease in advanced stage OC. Additionally, we wanted to examine the impact of practice change efforts to increase rates of RD0 and RD1 on outcomes [3]. Specifically, could survival be improved or maintained, despite using more complex surgery to render a higher percentage of patients with minimal RD?

2. Methods

This is a single institution, retrospective study that was approved by the Mayo Clinic Institutional Review Board. Perioperative patient characteristics and surgical outcome variables were collected in a prospective database on patients who underwent primary debulking surgery for stage IIIC OC from 2003 to 2011 at Mayo Clinic, Rochester, Minnesota. Patients with non-epithelial or borderline tumors, those classified as stage IIIC due to nodal disease only, patients who had received NACT, and patients who had denied access to their medical records for research purposes were excluded. In addition, patients included in the analysis were required to have abdominal disease >2 cm involving at least the omentum, diaphragm, splenic or hepatic capsule, or small or large bowel mesentery or serosa.

In 2006, after publication of a comparison of surgeon-dependent impact on prognosis after ovarian cancer surgery, we introduced measures to improve and standardize the approach to cytoreduction across our division. This included increased availability of surgeons focusing on maximum surgical efforts at cytoreduction, increased education of trainees and junior staff, discussion of outcomes at within the division of gynecologic oncology, and confidential feedback and benchmarking of individual surgeons [17].

Patient demographic and perioperative characteristics abstracted from the medical records are reported in Table 1. Four RD groups were defined: RD0, RD 0.1–0.5 cm, RD 0.6–1.0 cm, RD >1 cm based on largest residual tumor diameter. Surgical complexity was assigned using previously published methods and classified as low, intermediate, or high complexity surgery [18]. Complications occurring during the first 30 days after surgery were captured and graded according to the modified Accordion classification 0–4 scale [19]. In the modified Accordion classification system for postoperative complications, grade 3 complications included "all complications requiring endoscopic or interventional radiologic procedures or reoperation as well as complications resulting in failure of one or more organs" and death within 30 days was defined as a grade 4 complication [19]. When collecting data on complications, procedures that were cancer-related, i.e. diagnostic thoracentesis for staging, were not considered. Lastly, date and location of recurrence or date of last relevant clinical follow-up was recorded, as well as vital status, date of death, and date of last follow-up.

To assess the impact of the efforts to standardize the approach to cytoreduction, we divided the cohort into two time periods, cohort 1 included years 2003–2006 and cohort 2 included 2007–2011. The Wilcoxon rank-sum test was used to compare continuously scaled patient demographic and perioperative characteristics between the two time periods, and the chi-square test or Fisher's exact test were used to compare categorical patient characteristics and categorical outcomes between the time cohorts. Duration of follow-up was calculated from the date of primary cytoreduction surgery to the date of last follow-up or death. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test after restricting the follow-

Table 1
Patient demographics and perioperative characteristics.

	Total (N = 447)	Cohort 1 2003–2006 (N = 202)	Cohort 2 2007–2011 (N = 245)	p*
Age at surgery (years), mean (SD)	65.3 (11.4)	66.1 (11.8)	64.6 (11.0)	0.08
BMI (kg/m^2), mean (SD)	28.3 (6.5)	28.4 (6.7)	28.2 (6.3)	0.86
ECOG performance status, N (%)				0.34
0	317/446 (71.1)	149/201 (74.1)	168 (68.6)	
1	96/446 (21.5)	37/201 (18.4)	59 (24.1)	
2+	33/446 (7.4)	15/201 (7.5)	18 (7.3)	
ASA score, N (%)				0.18
<3	239 (53.5)	101 (50.0)	138 (56.3)	
≥3	208 (46.5)	101 (50.0)	107 (43.7)	
Preoperative CA-125 (U/mL), median (IQR)	688 (273, 1660)	729 (427, 1830)	607 (222, 1507)	0.01
Ascites, N (%)	294 (65.8)	140 (69.3)	154 (62.9)	0.15
Serous histology, N (%)	389 (87.0)	170 (84.2)	219 (89.4)	0.10
Residual disease, N (%)				<0.001
0	199 (44.5)	66 (32.7)	133 (54.3)	
0.1–0.5 cm	138 (30.9)	67 (33.2)	71 (29.0)	
0.6–1.0 cm	51 (11.4)	28 (13.9)	23 (9.4)	
>1 cm	59 (13.2)	41 (20.3)	18 (7.3)	
Surgical complexity, N (%)				<0.001
Low (0–3)	66 (14.8)	39 (19.3)	27 (11.0)	
Intermediate (4–7)	231 (51.7)	114 (56.4)	117 (47.8)	
High (8+)	150 (33.6)	49 (24.3)	101 (41.2)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; SD, standard deviation.

* Wilcoxon rank-sum p values presented for continuous variables and chi-square or Fisher's exact p values presented for categorical variables.