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Tertiary cytoreductive surgery in recurrent ovarian cancer: Selection criteria and survival outcome

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Abstract

Objectives. Studies of tertiary cytoreductive surgery (TCS) in recurrent epithelial ovarian cancer are limited, and appropriate patient selection remains a clinical challenge. We sought to evaluate the impact of TCS on survival and to determine predictors of optimal tertiary resection.

Methods. Between January 1997 and July 2004, 47 women with recurrent epithelial ovarian cancer underwent TCS at two institutions. All patients received initial platinum and taxane-based chemotherapy following primary cytoreductive surgery. Clinico-pathologic factors and survival were retrospectively abstracted from medical records. Optimal TCS was defined as microscopic residual disease.

Results. Thirty of 47 (64%) patients underwent optimal TCS. Size of tumor implants <5 cm on preoperative imaging was the only significant predictor of achieving optimal TCS. Overall survival after TCS was statistically longer in patients with microscopic versus macroscopic residual disease (24 versus 16 months, $p=0.03$). After controlling for age, time to progression and optimal TCS, only the presence of diffuse disease at tertiary exploration remained a significant poor predictor of survival. However, in a cohort of patients with limited disease implants, multivariate analysis indicated that optimal TCS retained prognostic significance as a positive predictor of survival. Twelve patients (26%) experienced severe postoperative complications, including six with pulmonary embolism, four with fistulae and two with postoperative myocardial infarctions.

Conclusions. Size of disease implants on preoperative imaging may guide the selection of candidates for TCS. In those patients with limited disease implants at laparotomy, optimal TCS is associated with improved survival.

Keywords: Epithelial ovarian cancer; Cytoreductive surgery; Recurrent disease

Introduction

Most women diagnosed with epithelial ovarian cancer present with advanced stage disease. While complete clinical remission can be achieved in up to 80% of these patients with cytoreductive surgery and combination chemotherapy, the typical clinical course of their disease is characterized by multiple recurrences [1–3]. Optimal management is less well defined in recurrent disease, and treatment is typically individualized based on factors such as progression-free interval, residual disease and quality of life. Management of recurrent disease may involve salvage chemotherapy, secondary tumor resection and/or radiation [4–13]. Several studies have examined secondary cytoreduction in the setting of recurrent ovarian cancer. In a review of the existing published data on salvage surgery in recurrent ovarian cancer, Munkarah and Coleman reported on the technical feasibility of further resection, with 67% of 631 patients undergoing "optimal" secondary cytoreduction (with the definition of "optimal" ranging from <0.5 cm to <2 cm in the 10 studies reviewed) [6]. Operative times, transfusion requirements and overall complication rates are comparable to those associated with primary surgery, indicating that these patients may undergo secondary tumor resection with acceptable morbidity [6,7]. The majority of these data also demonstrate a survival advantage for women in whom optimal secondary cytoreduction is achieved [6,12].

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Patients who enter a second remission following their initial recurrence will eventually relapse. Data examining the clinical benefit of additional cytoreductive procedures in this setting are limited, and there are no established guidelines to determine which patients may benefit from tertiary cytoreductive surgery (TCS). We hypothesized that in patients with a second disease recurrence, optimal tertiary surgical cytoreduction extends overall survival. Our objectives were to determine the feasibility and morbidity of TCS and examine the impact of optimal TCS on survival.

Patients and methods

The records of all patients with recurrent epithelial ovarian cancer or primary peritoneal carcinoma who underwent surgical procedures at Cedars-Sinai Medical Center and Johns Hopkins Hospital between January 1997 and July 2004 were reviewed under an IRB-approved protocol. All patients underwent secondary cytoreductive surgery at their first recurrence, followed by tertiary surgical exploration at their first suspected second recurrence of disease. Patients were taken to the operating room with the intent to perform complete resection of all macroscopic disease. Patients undergoing surgery for a primary diagnosis of bowel obstruction were excluded from review. While the clinicians at our institutions do not follow explicit criteria to select patients for tertiary cytoreduction, in general TCS is offered to patients with an extended disease-free interval after remission from secondary recurrence greater than 6 months, limited disease on imaging studies to less than 3 tumor sites, and performance status of 0 to 1.

Data were abstracted from medical records regarding preoperative clinical factors, such as age at time of second recurrence, performance status, initial treatment-free interval and treatment interval before tertiary cytoreductive surgery. Preoperative imaging details were also abstracted, including the number and size of disease sites. "Diffuse disease" was arbitrarily defined as ≥ 10 disease sites at exploratory laparotomy. Operative details such as blood loss, extent of cytoreductive surgery and size of the largest tumor nodule were also noted. The amount of residual tumor was considered microscopic when no visible disease remained at the conclusion of surgery, and more or less than 1 cm depending on the size of the remaining tumor nodules. We defined optimal TCS as microscopic residual disease. The postoperative course including length of hospital stay and complications within 30 days of surgery was recorded.

The stage at initial diagnosis was based on the system developed by the International Federation of Gynecology and Obstetrics (FIGO). The number, timing and type of chemotherapeutic regimens were abstracted in order to calculate the initial disease-free interval as well as the treatment interval before the TCS. Overall disease-specific survival (OS) was calculated from the time of the TCS until disease-related death.

Multivariate logistic regression was used to determine preoperative variables related to optimal TCS. Survival curves were estimated using the Kaplan–Meier method. The log rank test was used to compare survival curves across groups. Variables related to the hazard (risk) of death were assessed using Cox proportional hazards models. Hazard ratios and 95% confidence intervals were calculated for the significant predictor variables. A significance level of 0.05 was used throughout. Statistical calculations were performed using the software package SAS version 9.1 (SAS Institute, Cary, NC).

Results

Forty-seven patients who underwent TCS were identified. The median age at the time of the TCS was 58 (range, 28–77 years), and 92% (43/47) of patients had stage III or IV disease at initial diagnosis. The median time from secondary cytoreductive surgery (SCS) to TCS was 17 months (range, 6–66 months), with a median progression-free interval (PFI) before TCS of 11 months (range, 1–66 months). Computed tomography was the preoperative imaging modality of choice and was employed in 87% (41/47) of cases. The median number of disease sites identified on preoperative imaging was 4 (range, 1–diffuse).

A variety of cytoreductive surgical procedures were utilized during TCS, including small and large bowel resections, lymph node dissections, partial liver resections, splenectomies and genitourinary surgery. The median size of the largest tumor mass was 5 cm (range, 1–11). The median amount of blood loss was 250 cc (range, 5–1100). 64% (30/47) of patients underwent TCS to microscopic residual disease and 81% (38/47) had <1 cm of residual disease after TCS. The median hospital stay was 7 days (range 2–27).

To determine potential preoperative predictors of optimal TCS, multivariate logistic regression analysis was performed. After controlling for presence of ascites, initial disease-free interval, age at TCS and limited number of disease sites on preoperative imaging (less than 4), only size of tumor (less than 5 cm) remained as a statistically significant predictor of successfully resecting tumor at TCS to microscopic residual disease ($p=0.02$ and $p=0.03$, respectively; Table 1). The cutoff values for size of tumor and number of disease sites on preoperative imaging were chosen based upon the median values reported above.

To identify pre- and intraoperative findings that may influence survival after TCS, we performed both univariate and multivariate analyses. Univariate analysis identified that the presence of diffuse disease at laparotomy (defined as >10 disease sites) and suboptimal TCS were statistically significant negative predictors of survival ($p=0.008$ and 0.03, respectively). Age at TCS, time to progression, optimal cytoreduction at time of SCS and tumor size were not predictive of survival. In multivariate analysis, only the presence of diffuse disease remained significantly associated with a poorer outcome ($p=0.008$, HR = 2.78, 95% CI = 1.3–6.1; Table 2).

Thirty-four patients had <10 disease sites at tertiary exploration and were considered to have limited disease. To explore the impact of TCS on these patients, we examined a subset of patients with <10 disease sites at laparotomy. In this analysis of 34 patients, surgical resection of tumor implants to microscopic residual disease conferred a survival advantage both on univariate ($p=0.02$) and multivariate analysis ($p=0.02$, HR = 0.3, 95% CI = 0.11–0.85; Table 3).

Associations between extent of TCS and survival were further examined with Kaplan–Meier survival analyses. In

Table 1
Multiple logistic regression analysis of preoperative factors on ability to achieve optimal cytoreduction at tertiary exploration

Variable	OR	95% CI	p
Age at TCS [a]	1.02	0.96–1.08	n.s.
Initial treatment-free interval ≥ 12 months [b]	2.48	0.42–14.64	n.s.
Ascites [c]	1.00	0.18–5.64	n.s.
Number of lesions <4 [d]	1.36	0.30–6.13	n.s.
Size of largest tumor <5 cm [e]	7.42	1.66–33.27	0.009

[a] Analyzed as a continuous variable.
[b] 36 patients had an initial treatment free interval >12 months.
[c] 9 patients had ascites.
[d] 21 patients had number of lesions <4.
[e] 21 patients had size of their largest tumor <5 cm.