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Cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma

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Abstract

Objective. This study aims to identify favorable preoperative characteristics and examine the impact of secondary cytoreductive surgery on survival for patients with recurrent epithelial ovarian carcinoma.

Methods. Patients who underwent cytoreductive surgery for recurrent epithelial ovarian cancer were identified in our surgical database for the period 1988–2004. Patient charts were reviewed and data collected regarding patient demographics, surgical management, preoperative evaluation, perioperative complications, and oncologic outcome.

Results. Eighty-five patients met eligibility criteria. Preoperative factors that correlated with improved survival were disease-free interval of greater than 12 months ($p<0.01$) and residual disease after primary surgery of <2 cm ($p<0.02$). Other preoperative factors evaluated but not found significant included radiographic findings, physical findings, previous histology, stage, grade, previous chemotherapy, prior recurrence, and serum CA-125 level. Optimal resection to <1 cm residual disease was achieved in 86% of patients who had secondary cytoreduction. Small bowel and colon resection for cytoreduction occurred in 7% and 51% of patients, respectively. Operative complications occurred in 14% and postoperative complications occurred in 21% of patients. The median survival of patients who were optimally cytoreduced to <1 cm was 30 months compared to 17 months for patients with residual disease ≥1 cm ($p<0.05$). Operative factors that were evaluated and did not significantly effect survival were location of recurrence, presence of ascites, and extent of recurrence. Recurrent or progressive disease occurred in 75% of patients during follow-up.

Conclusion. When selecting patients for secondary cytoreduction, the most significant preoperative factors are disease-free interval and success of a prior cytoreductive effort. Once secondary cytoreductive surgery is attempted, the most important factor for improved survival is optimal cytoreduction. Of equal importance is counseling regarding the significant risk for bowel surgery, colostomy, and complications.

Keywords: Ovarian cancer; Secondary cytoreduction; Recurrent ovarian

Introduction

Annually there are 22,220 new cases of ovarian cancer in the United States and 16,210 deaths [1]. Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still present with advanced (Stages III–IV) disease [2]. In the setting of primary disease, optimal cytoreductive surgery (<1–2 cm) and platinum-based chemotherapy have been established as the most important components when treating advanced epithelial ovarian cancer [3–7]. The theoretic benefit from cytoreductive surgery relates to removing large tumor volumes that have a decreased growth fraction and poor blood supply, thereby improving the efficacy of chemotherapeutic agents [8].

Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced epithelial ovarian cancer will ultimately develop recurrent disease [9]. The management of recurrent ovarian cancer is less clear than that of primary disease. Available literature regarding secondary cytoreductive surgery is largely composed of retrospective studies and, more recently, several prospective studies [10–12]. Several studies have concluded that patients with platinum-resistant disease (recurrent disease within 6 months of completing

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Table 1
Intraoperative complications

Complication	Frequency (*n*)	Percent (%)
Enterotomy	7	8.3
Cystotomy	1	1.2
Hemorrhage*	1	1.2
Diaphragm injury	1	1.2
Vascular injury	1	1.2

*Hemorrhage defined as blood loss ≥2500.

treatment) do not benefit from secondary cytoreductive surgery [13,14]. Multiple other preoperative and operative factors have been evaluated to help delineate which patients will benefit from secondary cytoreductive surgery, but clear criteria for selection of patients remain unclear. This study was performed to help delineate factors that would improve survival in patients being evaluated for secondary cytoreduction. In addition, surgical procedures and complications are being reported so that appropriate preoperative counseling of patients can occur. Finally, from these patients for whom cytoreduction is determined to be beneficial, we hope to determine which operative factors influence survival.

Materials and methods

Institutional review board approval was obtained prior to initiating the study. Patients who underwent cytoreduction for recurrent ovarian cancer were identified from our gynecologic oncology surgical database for the period 1988–2004. Selection criteria for secondary cytoreductive surgery during the study interval included a disease-free interval ≥6 months, a Gynecologic Oncology Group performance status ≤2, radiographic and physical exam findings of an isolated site of recurrence, and absence of ascites. Exclusion criteria were those patients who underwent second-look surgery without cytoreduction, palliative surgery, and pathology other than epithelial ovarian cancer. Patient charts were reviewed and data were collected regarding patient demographics, preoperative evaluation, surgical management, perioperative complications, and oncologic outcome.

Board-certified gynecologic oncologists assisted by gynecologic oncology fellows performed the operations on all patients. Patients were staged according to FIGO criteria and optimal cytoreduction was defined as residual disease less than 1 cm maximum diameter. Patient follow-up consisted of further care at our institution and letters to patients that had gone elsewhere for care.

Cumulative data and subset analyses were performed using SPSS software (SPSS Inc., Chicago, IL). Using Kaplan–Meyer survival curves in addition to the log rank (Mantel-Cox) test, Breslow's ANOVA (Generalized Wilcoxon) test, and the Tarone-Ware test, the subsets of predictive factors for survival were compared, generating a chi-square value. These values were referenced according to their degrees of freedom and significance values of <0.05 were considered statistically significant.

Results

During the study period, 85 patients met eligibility criteria. The mean age was 61 years (range 35–87 years). Most patients were Caucasian (96%) and the mean body mass index was 24.6 kg/m^2 (range 19–46 kg/m^2). Comorbid medical conditions such as hypertension, diabetes, and coronary artery disease were present in 35% of patients. In our population, a personal history of breast and uterine cancer was reported in 10% and 5% of patients, respectively. Twenty percent of patients reported a family history of gynecologic or colon malignancies (breast 12.8%, ovarian 5.1%, colon 1.3%, uterine 1.3%).

The distribution of pathologic cell types was 88% serous, 3.7% mucinous, 2.4% endometrioid, 4.9% clear cell, and 1.2% undifferentiated. The stage distribution at the time of primary cytoreductive surgery was as follows; I in 12%, II in 13%, III in 65%, IV in 1.2%, and 8.4% were unstaged. The primary surgery was reported as optimal (<2 cm) in 76% of patients. Two patients had not received any prior chemotherapy. Of the patients that had received chemotherapy, 68% had 1 prior regimen (71.4% of which contained a platinum agent), 28% had two, and 1.2% had three prior regimens. The mean disease-free interval was 39 months (range 3–153) with the majority of patients (79.6%) having a disease-free interval of >12 months. At the time of recurrence, 41% of patients reported symptoms. The most common symptom experienced was abdominopelvic pain (26.5%). Other reported symptoms were abdominal pressure (4.8%), changes in bowel function (4.8%), and rectal bleeding (4.8%). The remaining 69% of asymptomatic patients were found to have recurrence based on physical exam, elevated tumor markers, or imaging. Cytoreduction was the indication for surgery in most patients (88%). However, 8% of patients had bowel obstruction and 3.6% were undergoing a second-look laparotomy and cytoreduction was attempted at that time.

At the time of surgery, localized disease was found in 62%, multiple areas of recurrence were found in 33%, and 4.8% had milliary disease. Preoperative radiographic and physical exam findings correlated with operative findings in 69% and 65%, respectively. The location of recurrence was the pelvis in 57%, abdomen in 12%, and both in 31%. Ascites (defined as >200 mL) was present in 3.6% of patients.

The mean operative time was 202 min (range 60–480 min) and the mean estimated blood loss was 696 mL (range 100–2500 mL). Small bowel and colon resection for cytoreduction occurred in 7% and 51% of patients, respectively. Both small bowel and colon resection were required in 9% of patients and an ostomy was placed in 20% of patients with colon resection. Optimal cytoreduction (<1 cm) was achieved in 86% of patients. Operative and postoperative complications are summarized in Tables 1 and 2, respectively. Patients had a mean hospital stay of 9 days (range 3–17 days), were on a regular diet by day 7 (range 3–14 days), and urinary catheters were removed on day 3 (range 1–14 days). Longer hospital stays were

Table 2
Postoperative complications

Complication	Frequency (*n*)	Percent (%)
Ileus	2	2.4
Sepsis	3	3.6
Bowel obstruction	1	1.2
Wound infection	4	4.8
Fistula	4	4.8
Renal failure	1	1.2
Anastomotic leak	1	1.2
ARDS*	1	1.2
Pneumonia	1	1.2

*ARDS (Acute Respiratory Distress Syndrome).

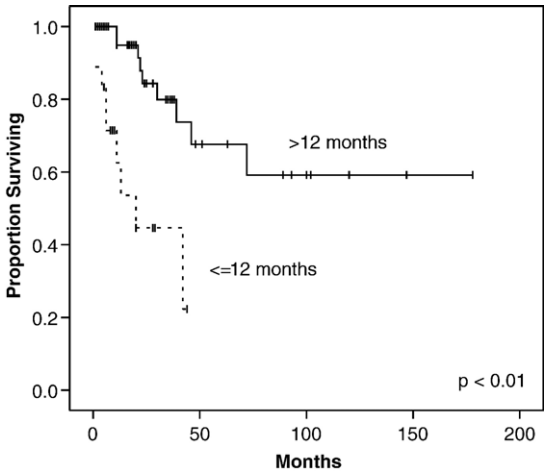

Fig. 1. Survival of patients by disease-free interval to secondary cytoreduction.

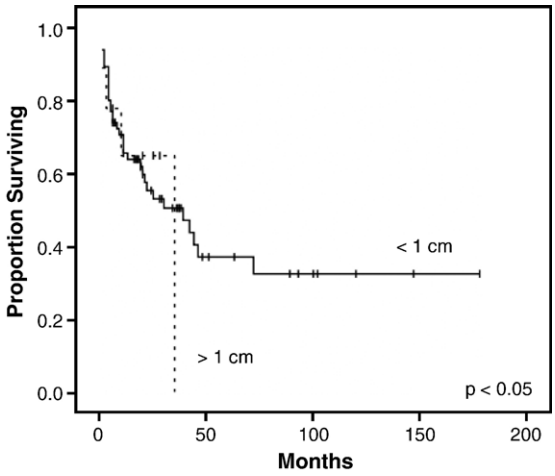

Fig. 3. Survival of patients by residual disease after secondary cytoreduction surgery.

associated with delayed return of bowel function in patients who underwent bowel resection.

Factors identified preoperatively that correlated with improved survival were disease-free interval of greater than 12 months ($p<0.01$) and residual disease after primary surgery of <2 cm ($p=0.02$) (Figs. 1 and 2). Other preoperative factors evaluated but not found to be statistically significant predictors of survival included radiographic and physical findings prior to surgery such as whether the disease was localized or not. Histology, stage, and grade at time of primary surgery as well as previous chemotherapy, prior recurrence, and serum CA-125 level were all found not to significantly affect survival in our patient population.

Median survival of patients who were optimally cytoreduced to <1 cm was 30 months compared to 17 months for those with residual disease ≥1 cm ($p<0.05$) (Fig. 3). When a subgroup analysis was performed comparing patients with macroscopic (<2 cm, <1 cm) vs. microscopic residual disease, there was no statistically significant difference in survival between the groups; however, there was a trend approaching statistical significance when comparing the >2 cm group with the microscopic disease group. Other operative factors that were evaluated but did not affect survival were location of recurrence (pelvic vs. abdominal), extent of recurrence (localized vs. multicentric) and presence of ascites. The mean follow-up was 28 months (range 1–178 months). Recurrent or progressive disease occurred in 75% of patients during the period of follow-up. The mean disease-free interval was 22 months (range 3–141 months).

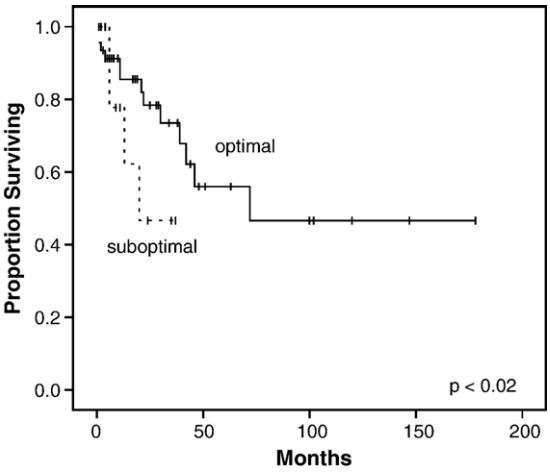

Fig. 2. Survival of patients by cytoreduction at primary surgery (optimal defined as <2 cm).

Conclusion

A consensus regarding the management of recurrent epithelial ovarian cancer, especially the role of secondary cytoreductive surgery, has yet to be reached. Much of the research is retrospective in nature and limited to small series [15–30].

More recently, several prospective studies have evaluated factors influencing survival in patients undergoing secondary cytoreductive surgery further clarifying and validating the large body of existing retrospective data [10–12].

Factors that affect survival in the setting of secondary cytoreduction can be divided into preoperative factors (Table 3) and operative factors (Table 4) [15–30]. One of the most studied factors is disease-free interval. In our study, improved survival was seen in patients with a disease-free survival of 12 months or more, with patients surviving 54 months with a disease-free interval of >12 months vs. 18 months in patients with a disease-free interval ≤12 months. Slight variation is seen among studies but consistently a longer disease-free interval has been associated with improved survival, with 12 months being the most common cut-off found to be significant (Table 3). Another preoperative factor found to be significant in one study is age, with patients less than 55 years old showing an improved survival. This was not confirmed in other studies, including the current series [18]. The volume of residual disease after the primary surgical cytoreduction (definition of which varies from <1–2 cm) has been shown in several studies, including this series, to significantly affect survival [15,17,18,21,22,30]. Larger tumor diameter at the time of recurrence has been

Table 3
Review of literature regarding influence of preoperative factors in patients undergoing secondary cytoreduction

Author (year)	*n*	Age	Initial cytoreduction status (optimal vs. suboptimal)	DFI	Histology	Grade	Pre-op CA-125	Salvage chemotherapy	Radiographic or physical findings	Size of recurrent tumor
Berek et al. [15]	32		19 vs. 5 months	<12 vs. >12 (9 vs. 16 months)						<5 cm (20 vs. 6 months)
Morris et al. [13]	30			NS						
Janicke et al. [17]	30		RR 2.7	<12 vs. >12 (8 vs. 29 months)						
Segna et al. [18]	100	<55 (27 vs. 14 months)	25 vs. 11 months	<12 months from primary surgery (9 vs. 23 months)						
Eisenkop et al. [19]	36			7–11 vs. 12–36 vs. >36 (19, 17, 43 months)						
Vaccarello et al. [20]	38		NS	NS	NS	NS				NS
Eisenkop et al. [10]	106	NS		6–12 vs. 13–36 vs. >36 (25, 44, 57 months)		NS	NS	When Not Given (48 vs. 25 months)	NS	<10 cm (37 vs. 35 months)
Gadducci et al. [21]	30	NS	37 vs. 19 months	<17.5 vs. >17.5 (15 vs. 25 months)	NS	NS				NS
Zang et al. [22]	60		NS	>12 months (RR.42)	NS	NS		NS		NS
Zang et al. [22]	106	NS	NS	≤12 vs. >12 (8 vs. 12 months)	NS	NS		NS		
Scarabelli et al. [11]	149	NS	NS	7–12 vs. 13–24 vs. >24 (2-year survival 22 vs. 63 vs. 23 months)	NS	NS		HR of 2.28 for patients with >1 prior chemo regimen		
Munkarah et al. [24]	25	NS	NS	NS	NS	NS				
Tay et al. [22]	46			<12 vs. 12–24 vs. >24 (6 vs. 11 vs. 39 months)		NS				
Zang et al. [12]	117	NS	NS	3–12 vs. 13–23 >24 (18, 26, 40 months)	NS	NS		NS		
Gronlund et al. [26]	38			>12 (HR 2.3)						
Güngör et al. [27]	44			NS						NS
Ayhan et al. (2005)	64	NS	30 vs. 18 months	≤12 vs. >12 (12 vs. 39 months)	Endometriod (OR 0.09)	NS		NS		NS
Chi et al. (2005)	153	NS	NS	6–12 vs. 13–30 vs. >30 (30, 39, 51 months)	NS	NS	NS		NS	
Onda et al. [30]	44	NS		<12 vs. ≥12 (23 vs. 47 months)	NS			NS		≥6 cm (RR 7.43)
Current study	85	NS	46 vs. 13 months	≤12 vs. >12 (18 vs. 54 months)	NS	NS	NS	NS	NS	

Not significant (NS), blanks indicate factors not evaluated in study Median survival expressed in months (if not available, then expressed in hazards ratio (HR), odds ratio (OR), or relative risk(RR)).

Table 4
Review of literature regarding influence of operative factors on survival for patients undergoing secondary cytoreduction

Author (year)	*n*	Optimal defined (cm)	Optimal (%)	Recurrence sites (median survival)	Absence of ascites (median survival)	Median survival effect of optimal cytoreduction
Berek et al. [15]	32	<1.5	38		18 vs. 5 months	16 vs. 9 months
Morris et al. [13]	30	≤2	57			NS
Janicke et al. [17]	30	≤2	47			29 vs. 9 months
Segna et al. [18]	100	<2	61			27 vs. 9 months
Eisenkop et al. [10]	36	No macroscopic	83			43 vs. 5 months
Gadducci et al. [21]	38	<0.05	37			23 vs. 9 months
Zang et al. [22]	106	No macroscopic	82	NS	NS	44.4 vs. 19.3 months
Zang et al. [22]	30	No macroscopic	57	Single vs. multiple (40 vs. 19 months)		37 vs. 19 months
Scarabelli et al. [11]	60	<1	38		13 vs. 6 months	19 vs. 8 months
Munkarah et al. [24]	106	≤1	43		14 vs. 7 months	20 vs. 8 months
Tay et al. [22]	149	No macroscopic	36			HR 2.65 for ≤1 and 5.79 for >1 cm
Zang et al. [12]	25	<2	72	NS		NS
Gronlund et al. [26]	46	No macroscopic	41			38 vs. 11 months
Güngör et al. [27]	117	≤1	62	Solitary vs. multiple (5-year survival 49.8 vs. 5.4%)	25 vs. 17 months	26 vs. 15 months
Ayhan et al. (2005)	38	No macroscopic	42	Single vs. multiple (HR 0.31)		52 vs. 20 months
Chi et al. (2005)	44	No macroscopic	77	NS		19 vs. 9 months
Onda et al. [30]	64	<1	83	NS		28 vs. 18 months
Chi et al. (2005)	153	≤0.05	52	Single vs. multiple vs. carcinomatosis (60 vs. 42 vs. 28 months)	NS	56 vs. 27 months
Onda et al. [30]	44	<1	84	Multiple (RR 3.73)	NS	NS
Current study	85	<1	86	NS	NS	30 vs. 17 months

Not significant (NS), blanks indicate factors not evaluated in study Median survival expressed in months (if not available, then expressed in hazards ratio (HR), relative risk (RR) or 5-year survival).

shown to adversely affect survival although this varies from 5–10 cm depending on the study [15,21,30]. Although not evaluated in most studies, it has been shown that salvage chemotherapy prior to cytoreduction adversely affects survival [21,24]. Other factors that have been evaluated but have shown little or no effect on survival include histology, tumor grade, serum CA-125 level, and preoperative radiographic and physical findings (Table 3) [15–30].

Factors that appear to affect survival at the time of secondary cytoreduction are summarized in Table 4. Optimal secondary cytoreduction has been one of the most consistent factors found to improve survival. The definition of optimal cytoreduction varies but as with primary cytoreduction, it appears that patients cytoreduced to microscopic disease or at least <1 cm consistently have improved survival [15,17–19,21–25,27–29,28–30]. The percent of patients who are optimally cytoreduced varies greatly from one study to another. However, there has been a trend towards more patients being optimally cytoreduced in recent series coinciding with mounting literature consistently demonstrating improved survival in patients optimally cytoreduced both in the primary and recurrent settings [15–30]. At the time of secondary surgery, the presence of ascites, multiple sites of recurrence, and large tumor volumes appears to adversely affect survival [15,21–24,28–30]. Our selection criteria during the period of data study were quite stringent as outlined in the Materials and methods section with solitary recurrence and absence of ascites being criteria for consideration of secondary cytoreduction. These factors must be considered when exploring a patient for possible secondary cytoreduction.

Patients undergoing secondary cytoreduction can expect a significant stay in the hospital; 9 days in our study which is similar to that reported by other studies [19,26]. Estimated blood loss and operative time in prior studies range from 450 to 680 cm^3 and 150 to 200 min, which are similar to our series [21,23,26,28,30]. In addition, the need for bowel surgery is frequent. In our study, the rates of colon, small bowel, and combined small bowel and colon resection were 51%, 7%, and 9%, respectively. The rates of bowel resection reported in other studies ranges from 20 to 33% requiring colon resection and 6 to 21% requiring small bowel resection [22,26,28–30]. In addition to bowel resection, ostomies were needed in 20% of our patients who had colon resection performed.

The main alternative to secondary cytoreduction is salvage chemotherapy alone. The EORTC (European Organization for the Research and Treatment of Cancer) has a trial addressing this issue (Protocol#55963). The study group in this trial consists of patients with recurrent ovarian cancer who received a minimum of three cycles of primary chemotherapy and had a disease-free interval of 12 months or greater. Patients were randomized to receive 6 cycles of platinum-based chemotherapy or 3 cycles of chemotherapy followed by surgical exploration and an additional 3 cycles of chemotherapy. This trial is currently closed to enrollment and is awaiting data maturation and final results. The GOG (Gynecologic Oncology Group) is in the process of designing a protocol (protocol #213)

to evaluate the best way to manage recurrent ovarian and primary peritoneal cancer after having a complete response to primary treatment.

Until these or other study results are available, the current literature will have to be used to determine which patients should be selected for cytoreductive efforts. The preoperative factor that best predicts improved survival after secondary cytoreductive surgery is a disease-free interval of >12 months. Factors associated with a low likelihood of benefit include prior suboptimal cytoreductive surgery, large tumor size, and extensive disease at the time of recurrence. Once secondary cytoreductive surgery is determined to be potentially beneficial based on preoperative factors, an aggressive surgical approach should be undertaken since optimal cytoreduction to <1 cm or microscopic disease improves survival.

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