HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2016 April 25.

Published in final edited form as:

Gynecol Oncol. 2010 March ; 116(3): 351–357. doi:10.1016/j.ygyno.2009.11.022.

The Effect of Primary Cytoreduction on Outcomes of Patients with FIGO Stage IIIC Ovarian Cancer Stratified by the Initial Tumor Burden in the Upper Abdomen Cephalad to the Greater Omentum

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Abstract

Objective—Our objective was to analyze the effect of surgical outcome on progression-free survival (PFS) and overall survival (OS) of patients with advanced ovarian carcinoma stratified by the initial presence and volume of upper abdominal disease cephalad to the greater omentum (UAD) found at the time of exploration.

Methods—We evaluated all patients with FIGO stage IIIC ovarian carcinoma who underwent primary cytoreduction followed by platinum-based chemotherapy at our institution between

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Presented at the 40th Annual Meeting on Women's Cancer, February 5–8, 2009, San Antonio, TX.

CONFLICT OF INTEREST STATEMENT

1. Oliver Zivanovic, MD: no conflicts of interest to declare
2. Camelia Sima: no conflicts of interest to declare
3. Alexia Iasonos, PhD: no conflicts of interest to declare
4. William J. Hoskins, MD: no conflicts of interest to declare
5. Pavani R. Pingle: no conflicts of interest to declare
6. Mario MM Leitao Jr, MD: Genzyme – consultant/speaker; Intuitive Surgical – surgical proctor
7. Yukio Sonoda, MD: Plasma Surgical – research support; Covidien – consultant; Genzyme – speaker
8. Nadeem R. Abu-Rustum, MD: no conflicts of interest to declare
9. Richard R. Barakat, MD: no conflicts of interest to declare
10. Dennis S. Chi, MD: Genzyme – speaker

01/1989 and 12/2006. The effect of surgical outcome was investigated using a time-to-event analysis. A Cox proportional hazards model was fit using clinical, surgical, and postoperative variables.

Results—We identified 526 evaluable patients. Optimal versus suboptimal cytoreduction was significantly associated with improved median PFS and OS in patients with no, minimal (≤1 cm), and bulky (>1 cm) UAD. On multivariate analysis, patients with bulky UAD who underwent optimal cytoreduction had a 28% decreased risk of relapse (Hazard Ratio, 0.72; 95% Confidence Interval: 0.53–0.99; *P*=0.04) and a 33% decreased risk of death (Hazard Ratio, 0.67; 95% Confidence Interval: 0.47–0.96; *P*=0.03) compared to patients who underwent suboptimal cytoreduction.

Conclusion—The presence of large-volume disease found during surgical exploration does not preclude the benefit of optimal cytoreduction. The findings support the management strategy of maximizing surgical efforts with increasing tumor burden in patients with stage IIIC ovarian cancer. Prospective studies are needed to more precisely quantify tumor burden and accurately determine the specific impact of cytoreduction on outcome.

Keywords

upper abdominal disease cephalad to the greater omentum; upper abdominal disease; ovarian cancer; survival; cytoreduction; surgery

Introduction

Although the use of postoperative chemotherapy for the treatment of advanced ovarian cancer is based on prospective randomized trials [1–6], the rationale for surgery is derived mainly from retrospective data demonstrating that the amount of residual disease after cytoreductive surgery inversely correlates with progression-free and overall survival [7–15]. It is debatable whether it is the surgical procedure itself that is responsible for the superior outcome associated with small-volume residual disease or whether the ability to achieve minimal residual disease identifies a biologically more favorable patient subgroup with excellent response to postoperative chemotherapy [16]. In fact, the prognostic relevance of residual disease is so powerful that in today's practice patients are stratified to postoperative chemotherapy treatments or randomized clinical trials based on the amount of residual disease remaining after surgery [1,6]. Currently, optimal surgical outcome is defined as disease of 1 cm or less in single largest diameter, whereas residual tumor exceeding 1 cm in single largest diameter is defined as a suboptimal surgical outcome.

Advances in surgical training, technique, and perioperative care have allowed surgeons to maximize cytoreductive efforts in patients with advanced stage IIIC and IV ovarian cancer, enabling them to increase the rate of optimal cytoreduction and target anatomical sites previously thought to be unresectable. Many authors now propose a new, more comprehensive approach to cytoreduction [8,17–23]. However, there is controversy as to how much surgical effort should be undertaken to achieve optimal residual disease status before reaching the point of subjecting the patient to the morbidity of a surgical procedure that is of no or only minimal oncologic benefit. A Gynecologic Oncology Group (GOG)

study demonstrated that patients with stage III disease presenting with large-volume ovarian cancer before undergoing optimal cytoreduction had a worse prognosis than patients found to have small-volume disease at the time of exploration [24]. The Scottish Randomized Trial in Ovarian Cancer (SCOTROC) showed that a clinically significant progression-free survival (PFS) benefit with optimal surgery among patients with stage IC to IV disease was limited to patients with less-advanced disease (as defined by clinical and biologic risk factors) [25]. Eisenkop et al. observed that the need to remove a large number of peritoneal implants correlates with biological aggressiveness and diminished survival, but not significantly enough to preclude long-term survival or justify abbreviation of the operative effort [20,26].

Advanced International Federation of Gynecology and Obstetrics (FIGO) stage IIIC ovarian cancer is heterogenous, ranging from limited intra-abdominal disease to diffuse carcinomatosis involving the majority of peritoneal surfaces (Figure 1). Disease involving the upper abdomen cephalad to the greater omentum is frequently seen in patients with stage IIIC ovarian cancer. It has been cited as the principle obstacle to achieving an optimal cytoreductive outcome. For the purposes of this analysis, we use the presence and volume of upper abdominal disease cephalad to the greater omentum (UAD) as a marker for the general intra-abdominal tumor burden and carcinomatosis. This is based on data demonstrating that UAD is associated with adverse prognostic and tumor-volume factors such as large-volume ascites, highly elevated serum CA-125 levels, and a higher rate of suboptimal cytoreduction [27]. In addition, as the tumor volume in the upper abdomen increases, more surgical effort is necessary to achieve optimal cytoreduction. In patients with bulky UAD, comprehensive surgical strategies such as radical pelvic surgery, bowel surgery, and resection of upper abdominal lesions involving the diaphragm, spleen, liver, and porta hepatis are frequently necessary.

We sought to analyze the effect of optimal cytoreduction on PFS and OS in patients with FIGO stage IIIC ovarian cancer stratified by the initial presence and volume of UAD.

Methods

We evaluated all patients with FIGO stage IIIC ovarian cancer undergoing primary cytoreductive surgery followed by intravenous or intraperitoneal platinum-based chemotherapy at our institution from January 1, 1989 to December 31, 2006. Any missing data were retrospectively collected from the electronic patient records. Patients who underwent primary cytoreductive surgery at outside institutions, those who were treated with neoadjuvant chemotherapy, and those with non-epithelial histologic subtypes or borderline cancers were excluded.

The presence and size of UAD at the beginning of exploratory surgery was collected from the attending surgeon’s dictated operative report and a standardized postoperative checklist. UAD was defined as metastatic implants involving the diaphragm, liver, porta hepatis, spleen, pancreas, stomach, celiac axis, and lesser sac. Plaque-like confluent disease was considered as bulky disease irrespective of thickness. Optimal surgical outcome was defined as no residual tumor lesion measuring greater than 1 cm in single largest dimension at the completion of surgery. The study group was divided into three groups based on the presence

and size of disease cephalad to the greater omentum found at the beginning of the operative procedure (before undergoing cytoreductive surgery) — the first group included patients with no visible or palpable UAD on exploration; the second group consisted of patients with minimal UAD (1 cm or less); and the last group consisted of patients with bulky UAD (larger than 1 cm) (Figure 1).

Progression of disease was determined based on the definitions outlined by the Gynecologic Cancer Intergroup [28,29]. A patient was considered to have progression on the basis of either the objective Response Evaluation Criteria in Solid Tumors (RECIST) or serum CA-125 criteria. If both events were documented, the earlier event was chosen to represent the date of progression. When determined by CT scan, the date of progression was documented when one or more new lesions was detected or known existing lesions increased in size. When determined by CA-125 value, the date of progression was documented if the CA-125 value was greater than or equal to two times the nadir value (in patients with abnormal CA-125 values) or if it was two times or greater than the upper normal limit (35 U/ml) of CA-125 (in patients whose CA-125 normalized during treatment).

Statistical Methodology

The effect of surgery was investigated using a time to event analysis. PFS was defined as the time interval from the date of surgery to the progression of disease, death or last available follow-up, whichever occurred first. OS was defined as the time interval from the date of surgery to the date of death or last follow-up, whichever occurred first. Kaplan-Meier estimates of PFS and OS stratified by the level of cytoreductive outcome (no gross residual disease, macroscopic ≤1 cm residual disease, >1 cm residual disease) were calculated and compared using the log-rank test separately in the subgroups categorized by the presence and volume of UAD.

A multivariate Cox proportional hazards model was fit to investigate the effect of surgery on PFS and OS by different levels of UAD tumor volume found at the beginning of the surgical procedure. Beginning in 2000, a change in surgical management towards more comprehensive cytoreduction targeting the upper abdomen was initiated at our institution, resulting in significantly higher rates of optimal cytoreduction [17,18,27]. Therefore, we adjusted the model for the year of surgery (1989–1999 versus 2000–2006) through stratification. The following potential confounders were controlled for: age at the time of surgery, histology type (serous versus others), ascites volume, chemotherapy regimen (taxane versus no taxane), and the number of chemotherapy cycles (>6 versus ≤6 cycles). Ascites volume was included in the model on a logarithmic scale, while the number of chemotherapy cycles and chemotherapy regimens were treated as time-dependent covariates. Because patients treated by the same surgeon are likely to have correlated surgical outcomes, we incorporated within-surgeon clustering into our analyses using a generalized estimating equations approach, and we corrected the variance of our estimates using robust sandwich variance estimators [30]. All associations were regarded significant if the P value was <0.05. All P values are two-sided. The statistical analyses were performed using SAS version 9.1 (SAS Institute, Carey, North Carolina)

Results

We identified 535 patients with advanced FIGO stage IIIC epithelial ovarian cancer who underwent primary cytoreduction followed by platinum-based chemotherapy during the study period. Nine patients were excluded based on missing intraoperative information regarding the presence and volume of UAD, leaving 526 evaluable patients for the analysis. Patient and clinical characteristics, stratified by volume of UAD, are listed in Table 1. The majority of tumors were high grade (82%) and of serous histology (78%). Most patients received systemic platinum and taxane-based chemotherapy postoperatively.

The percentage of patients with tumors of serous histology, the median preoperative CA-125 level, the median ascites volume, and the rate of suboptimal cytoreduction increased as the initial volume of UAD increased. Optimal cytoreduction was achieved in 104/125 (83%), 106/158 (67%), and 104/243 (42%) patients with no, minimal, and bulky UAD, respectively ($P<0.0001$). There were no significant differences in postoperative chemotherapy treatment, number of cycles given, and rate of consolidation therapy administered among the three groups . Table 2 shows the rate of cytoreductive outcomes and the distribution and volume of UAD during the study period. The frequency and degree of UAD did not change while the rate of optimal cytroreduction increased over time.

The median follow-up time for patients without progression or death was 54 months (range, 8 to 186 months). The median PFS was 17 months (95% Confidence Interval [CI]: 16–19 months) and the median OS was 50 months (95% CI: 45–54 months). Figures 2A, 2B, and 2C show the estimated PFS of patients stratified by disease volume involving the upper abdomen cephalad to the greater omentum found at the time of exploration. Optimal versus suboptimal cytoreduction was significantly associated with improved median PFS in patients with *no UAD* (30 months versus 14 months, $P<0.001$) and *minimal* (≤1 cm) *UAD* (21 months versus 11 months, $P<0.001$). In the highest-risk group of patients with *bulky UAD*, optimally cytoreduced patients had a median PFS of 19 months compared to 13 months for those who were left with suboptimal residual disease ($P=0.02$). In addition, optimal cytoreduction was associated with improved OS in patients with *no UAD* (80 months versus 41 months, $P<0.001$), *minimal UAD* (56 months versus 26 months, $P<0.001$) and *bulky UAD* (58 months versus 38 months, $P=0.003$), respectively.

Patients who were left with suboptimal residual disease had a comparable low median PFS (*no UAD*, 14 months, 95% CI: 10–18 months; *minimal UAD*, 11 months, 95% CI: 9–13 months; and *bulky UAD*, 13 months, 95% CI: 12–16 months; $P=0.41$) and OS (*no UAD*, 41 months, 95% CI: 10–53 months; *minimal UAD*, 26 months, 95% CI: 17–35 months; and *bulky UAD*, 38 months, 95% CI: 33–45 months; $P=0.26$), irrespective of the initial tumor burden that was found at the beginning of cytoreductive surgery. Among patients who underwent optimal cytoreduction, the median PFS of patients who had no visible or palpable UAD on exploration was superior to that of patients who were found to have more extensive tumor involvement at the time of exploration (*no UAD*, 30 months, 95% CI: 23–45 months; *minimal UAD*, 21 months, 95% CI: 18–24 months; and *bulky UAD*, 19 months, 95% CI: 15–24 months; $P=0.001$). A similar trend was observed with regards to OS, although it did not reach statistical significance (*no UAD*, 80 months, 95% CI: 66–134 months; *minimal*

UAD, 56 months, 95% CI: 49–81 months; and *bulky UAD*, 58 months, 95% CI: 50–70 months; *P*=0.17).

We separately analyzed patients who underwent a complete gross tumor resection (N=93). The difference in PFS and OS remained in favor of patients who were found to have no visible or palpable UAD on exploration, and the difference was of similar magnitude as in the main analysis. Among patients who underwent a complete gross resection, patients without UAD (N=61) had a median PFS of 33 months compared to a median PFS of 22 months for patients with both minimal (N=9) and bulky UAD (N=23), respectively (*P*=0.03).

A Cox proportional hazards model was fit to investigate the effect of cytoreductive outcome on PFS and OS by levels of initial tumor volume, while accounting for potential confounders (Table 3). On multivariate analysis, the risk of relapse was significantly decreased in patients who underwent optimal versus suboptimal cytoreduction, irrespective of the volume of UAD that was found before cytoreduction. Although the magnitude of surgery effect decreased as the level of initial tumor volume increased, the effect remained significant even in patients with heavy tumor burden and carcinomatosis. Patients with bulky UAD who were left with optimal residual disease at the completion of cytoreductive surgery had a 28% decreased risk of relapse compared to patients who underwent suboptimal cytoreduction (Hazard Ratio 0.72; 95% CI: 0.53–0.99; *P*=0.04) and a 33% decreased risk of death (Hazard Ratio, 0.67; 95% CI: 0.47–0.96; *P*=0.03) compared to patients who underwent suboptimal cytoreduction.

Discussion

We report a single-institution experience of surgical cytoreduction in a large number of patients with FIGO stage IIIC ovarian cancer treated with postoperative platinum-based chemotherapy over a 17-year period. We have utilized the presence and volume of UAD cephalad to the greater omentum as a marker for the general burden of disease and carcinomatosis. This model is a simple approach that lacks the complex developmental and tumor biologic features of advanced ovarian cancer. However, UAD is associated with adverse tumor biologic and tumor volume criteria of advanced ovarian carcinoma. This is supported by the results of this analysis, highlighting the high-risk criteria of patients with bulky UAD. Second, the presence of bulky UAD generally requires the utilization of more comprehensive surgical strategies to achieve optimal cytoreduction in addition to standard surgical management [17,18,27]. We acknowledge that the documentation of findings on laparotomy (e.g., size and location of UAD) depends on the individual surgeon. An alternative, less subjective strategy would be to stratify by the documentation of procedures necessary to achieve optimal cytoreduction. However, this strategy contains an inherent selection bias, because ideally surgeons limit the use of more extensive procedures to patients who are felt to be optimally resectable, potentially over-representing patients with a better prognosis.

The current study is limited by its retrospective nature, and is thus prone to selection bias, other potential confounders and the long study period in which postoperative fist-line chemotherapy experienced a change in the 1990s with the introduction of taxanes and a surgical management shift towards more comprehensive procedures in 2000, which resulted

in increased optimal cytoreduction rates. Our analysis, however, takes this into account by using an adjusted time-to-event-analysis that allowed an extension of the Cox Proportional Hazards Model for time-dependent variables (chemotherapy regimen and number of cycles) in addition to adjusting for surgeon effects and year of surgery. Furthermore, the documented distribution and volume of UAD did not change during this time period.

The effect of UAD and optimal cytoreduction was analyzed in a in a subset of patients treated after 2000 (data not shown) in order to assess whether a similar trend was observed in a more homogenous cohort with regards to cytoreductive effort and postoperative treatment. The hazard ratios were in the same direction and magnitude, although the confidence intervals were too wide to be informative due to the reduction in sample size (291 patients).Because the multivariable model includes time-dependent variables (postoperative chemotherapy and number of cycles), prognostic variables (age, ascites, histology), correction for within-surgeon clustering and year of surgery, it provides meaningful information about whether cytoreductive surgery has an effect on PFS following primary therapy. However, due to the lack of information on subsequent treatment strategies after recurrence, the interpretation of the effect on OS is limited. Thus, in this study it is not possible to distinguish the effect of cytoreductive surgery on OS from the potential influence of other subsequent treatments.

Among this large group of patients with advanced stage IIIC disease, optimal cytoreduction was associated with a reduced risk of relapse and death, irrespective of the initial presence and volume of disease cephalad to the greater omentum that was found at the beginning of the surgical procedure. While the benefit of optimal cytoreduction on PFS and OS decreased with increasing initial tumor volume, optimal cytoreduction still conferred a statistically significant PFS and OS benefit in the highest-risk group of patients with large-volume UAD and presumed adverse tumor biology. In this group, the median PFS of 19 months and the median OS of 58 months are comparable to that of optimally resected stage III patients in the standard arms of GOG protocols 172 and 158 [1,6], which also included patients with less advanced stage IIIA and IIIB disease.

In the current analysis, the rate of complete gross resection was significantly higher in patients who were found to have no visible or palpable UAD on exploration when compared to patients with more initial tumor involvement, and one could argue that this is the reason for the improved PFS between the different groups. However, a significant difference in median PFS and OS after complete gross resection remained in favor of patients without initial UAD found at the time of exploration compared to completely resected patients with minimal or bulky UAD. This finding supports the hypothesis that stage IIIC patients presenting with large-volume ovarian cancer represent patients with more aggressive ovarian cancer phenotypes or patients who may have had their disease for a longer period of time, allowing for advanced growth and implantation.

The effort and extent of cytoreductive surgery is heterogenous, ranging from standard cytoreductive procedures to complex procedures involving multi-organ resection that are generally long and require the use of upper abdominal surgery. These more comprehensive procedures are associated with longer operating times, higher blood loss, and the potential

for “non-gynecologic” complications that add to the usually encountered perioperative morbidity. However, in the hands of an experienced and devoted cytoreductive team (surgeon, anesthesiologist, nursing), they are readily manageable and acceptable, without significant delay of postoperative chemotherapy in the majority of cases [18,31–33].

In conclusion, residual disease status at the beginning of postoperative chemotherapy remains an important prognostic factor in patients with stage IIIC epithelial ovarian cancer. The magnitude of the effect of optimal cytoreductive outcome varies with variable degrees of upper abdominal disease involvement. While the presence of large-volume disease decreases the benefit of optimal cytoreduction, it does not eliminate it. These findings support the management strategy of maximizing surgical efforts with increasing tumor burden in patients with stage IIIC ovarian cancer. Prospective studies are needed to more accurately quantify tumor burden and more precisely determine the specific impact of cytoreduction on outcome.

Acknowledgments

The authors would like to thank George Monemvasitis for his editorial assistance in the preparation of the manuscript and Terry Helms for her contribution to the illustrations.

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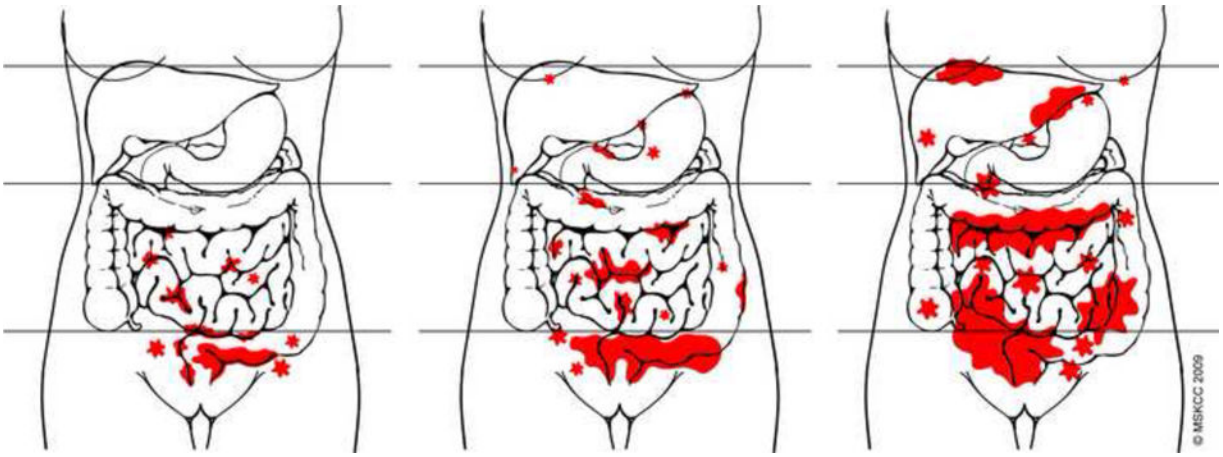

Figure 1.

Three different groups of patients presenting with FIGO stage IIIC ovarian carcinoma (uterus, fallopian tubes/ovaries, and omentum removed) and their peritoneal disease distribution at the beginning of the operative procedure. (A), upper abdomen cephalad to the greater omentum; (B), mid-abdomen; (C), pelvis; UAD, upper abdominal disease cephalad to the greater omentum

UAD is defined as metastatic implants involving the diaphragm, liver, porta hepatis, spleen, pancreas, stomach, celiac axis, and lesser sac. Group 1 includes patients without visible or palpable UAD (Region A) at the time of exploration. Group 2 consists of patients with minimal UAD (1 cm or less), and Group 3 consists of patients with bulky UAD (larger than 1 cm).

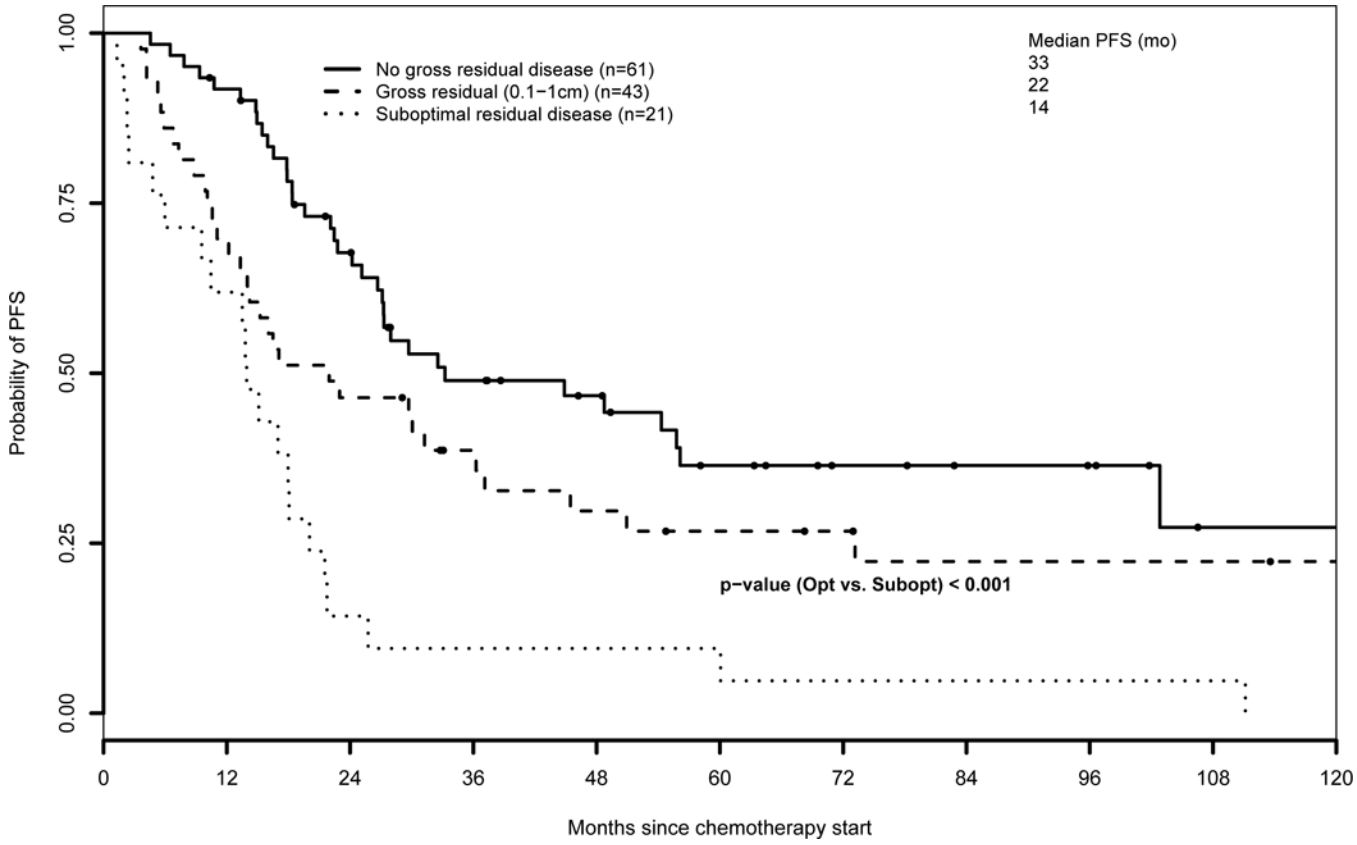

Figure 2A.

Estimated progression-free survival of patients with no UAD stratified by residual disease (optimal versus suboptimal). Patients who were optimally cytoreduced were further stratified into two groups based on the amount of residual disease remaining after cytoreductive surgery (no gross residual disease versus minimal residual disease of 1 cm or less in maximum diameter).

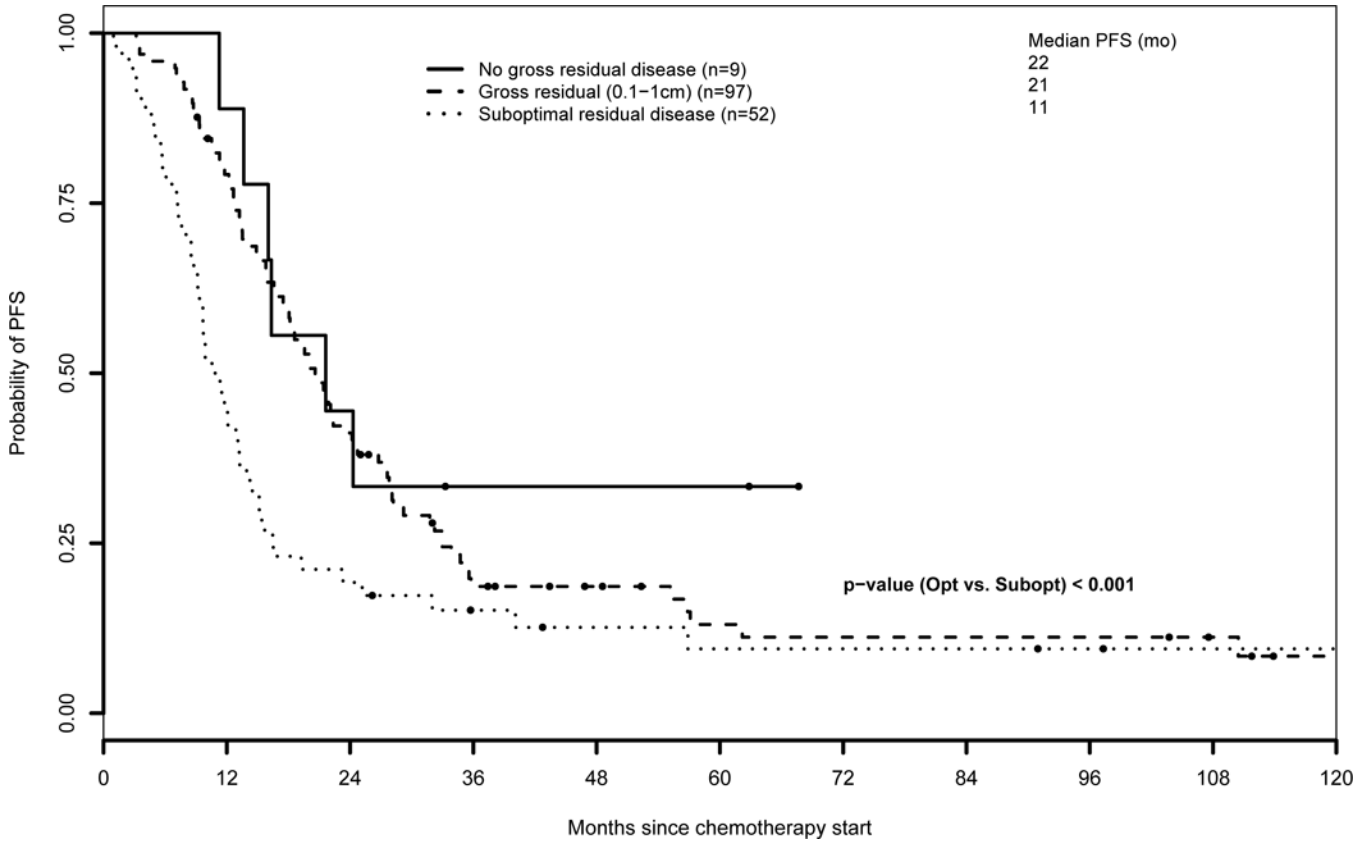

Figure 2B.

Estimated progression-free survival of patients with minimal UAD stratified by residual disease (optimal versus suboptimal). Patients who were optimally cytoreduced were further stratified into two groups based on the amount of residual disease remaining after cytoreductive surgery (no gross residual disease versus minimal residual disease of 1 cm or less in maximum diameter).

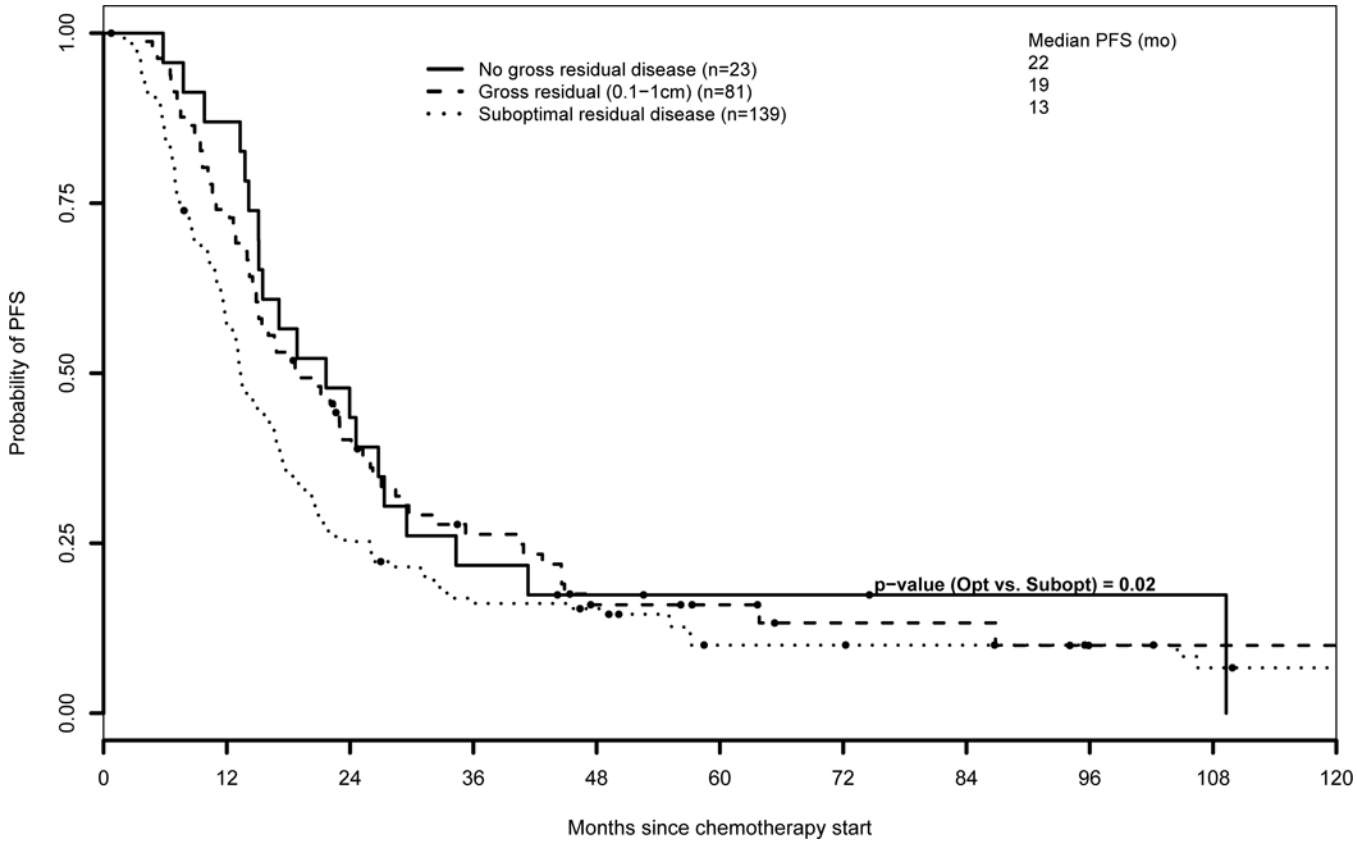

Figure 2C.

Estimated progression-free survival of patients with bulky UAD stratified by residual disease (optimal versus suboptimal). Patients who were optimally cytoreduced were further stratified into two groups based on the amount of residual disease remaining after cytoreductive surgery (no gross residual disease versus minimal residual disease of 1 cm or less in maximum diameter).

Table 1

Patient and clinical characteristics stratified by the presence and volume of upper abdominal disease cephalad to the greater omentum

Variable N	All Patients 526	No UAD 125	Minimal UAD 158	Bulky UAD 243	*P**
Age, years					
Median (range)	61 (25–88)	59 (25–87)	60 (25–88)	61 (26–87)	0.44
Histology					
Serous	408 (78%)	87 (70%)	118 (75%)	203 (84%)	0.006
Others	116 (22%)	38 (30%)	40 (25%)	40 (16%)	
Tumor grade					
High	431 (82%)	95 (76%)	133 (84%)	203 (84%)	0.14
Other	95 (18%)	30 (24%)	25 (16%)	40 (16%)	
Preoperative CA-125, U/ml					
Median (range)	902 (15–49,000)	393 (15–49,000)	1,000 (18–29,100)	1,128 (16–38100)	<0.001
Ascites volume, ml					
Median (range)	1000 (0–17,700)	50 (0–9,500)	1000 (0–15,000)	2,000 (0–17,700)	<0.001
Residual tumor size					
no gross	93 (18%)	61 (49%)	9 (6%)	23 (9%)	<0.001
0.1–1.0cm	221 (42%)	43 (34%)	97 (61%)	81 (33%)	
> 1.0 cm	212 (40%)	21 (17%)	52 (33%)	139 (57%)	
Postoperative chemotherapy					
IV platinum plus taxane	401 (76%)	93 (74%)	126 (80%)	182 (75%)	0.81
IV platinum plus other	88 (17%)	21 (17%)	23 (15%)	44 (18%)	
IP platinum plus taxane	29 (6%)	8 (6%)	7 (4%)	14 (6%)	
Missing	8 (2%)	3 (2%)	2 (1%)	3 (1%)	
Number of cycles					
Median (range)	6 (0–12)	6 (0–10)	6 (0–12)	6 (0–12)	0.14
Consolidation chemotherapy					
Yes	253 (48%)	57(46%)	77 (49%)	119 (49%)	0.97
No	251 (48%)	59 (47%)	75 (47%)	117 (48%)	
Missing	22 (4%)	9 (7%)	6 (4%)	7 (3%)	

UAD, upper abdominal disease cephalad to the greater omentum; IV, intravenous; IP, intraperitoneal

* The *P* value refers to the comparison of the three groups (no UAD, minimal UAD, and bulky UAD)

Table 2

The rate of optimal cytoreduction and the frequency and volume of upper abdominal disease cephalad to the greater omentum during the study period

	Cytroreductive outcome, n (%)			Frequency and volume of UAD, n (%)			
Time period	**Optimal**	**Suboptimal**	**Total**	**No UAD**	**Minimal UAD**	**Bulky UAD**	**Total**
1989–1991	15 (34%)	29 (66%)	44	11 (25%)	11 (25%)	22 (50%)	44
1992–1994	19 (30%)	45 (70%)	64	13 (20%)	14 (22%)	37 (58%)	64
1995–1997	28 (44%)	36 (56%)	64	20 (31%)	23 (36%)	21 (33%)	64
1998–2000	47(52%)	44 (48%)	91	16 (18%)	38 (42%)	37 (41%)	91
2001–2002	67 (78%)	19 (22%)	86	24 (28%)	24 (28%)	38 (44%)	86
2003–2004	83 (81%)	19 (19%)	102	22 (22%)	36 (35%)	44 (43%)	102
2005–2006	55 (73%)	20 (27%)	75	19 (25%)	12 (16%)	45 (59%)	75
Total	314 (60%)	212 (40%)	526	125 (24%)	158 (30%)	243 (46%)	526

Table 3

Multivariate Cox proportional hazards model*: Impact of cytoreductive outcome in relation to initial tumor burden on progression-free survival and overall survival

	Progression-free survival		Overall survival	
Parameter	**Hazard Ratio (95% CI)**	***P* value**	**Hazard Ratio (95% CI)**	***P* value**
Age (5-year increments)	1.06 (1.01–1.10)	0.02	1.14 (1.08–1.20)	<0.001
Ascites volume**	1.09 (1.05–1.13)	<0.001	1.11 (1.06–1.16)	<0.001
Taxane, yes versus no	0.62 (0.47–0.82)	0.001	0.49 (0.36–0.66)	<0.001
Chemotherapy cycles, ≥6 *versus* <6	1.38 (0.94–2.03)	0.12	1.23 (0.79–1.20)	0.36
Histology, serous versus non-serous	0.88 (0.70–1.12)	0.27	0.83 (0.62–1.10)	0.19
No UAD				
Optimal versus suboptimal	0.29 (0.18–0.48)	<0.001	0.29 (0,16–0.53)	<0.001
Minimal UAD				
Optimal versus suboptimal	0.56 (0.37–0.86)	0.008	0.42 (0.26–0.67)	<0.001
Bulky UAD				
Optimal versus suboptimal	0.72 (0.53–0.99)	0.04	0.67 (0.47–0.96)	0.03

CI, Hazard Ratio Confidence Interval; UAD, upper abdominal disease cephalad to the greater omentum

*adjusted for time period (1989–1999 versus 2000–2006); robust variance estimate used to correct for within-surgeon clustering

**Logarithmic scale