Gynecologic Oncology 114 (2009) 26–31

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm ☆

Dennis S. Chi [a,*], Eric L. Eisenhauer [a], Oliver Zivanovic [a], Yukio Sonoda [a], Nadeem R. Abu-Rustum [a], Douglas A. Levine [a], Matthew W. Guile [b], Robert E. Bristow [b], Carol Aghajanian [c], Richard R. Barakat [a]

[a] Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[b] Department of Obstetrics and Gynecology, Johns Hopkins Medical Center, Baltimore, MD 21287, USA
[c] Solid Tumor Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

ARTICLE INFO

Article history:
Received 16 December 2008
Available online 23 April 2009

Keywords:
Ovarian cancer
Cytoreduction
Debulking
Survival

ABSTRACT

Objective. To determine the impact on progression-free survival (PFS) and overall survival (OS) of a programmatic change in surgical approach to advanced epithelial ovarian cancer.

Methods. Two groups of patients with stage IIIC and IV ovarian, tubal, and peritoneal carcinoma were compared. Group 1, the control group, consisted of all 168 patients who underwent primary cytoreduction from 1/96 to 12/99. Group 2, the study group, consisted of all 210 patients who underwent primary surgery from 1/01 to 12/04, during which time a more comprehensive debulking of upper abdominal disease was utilized.

Results. There were no differences between the groups in age, primary site of disease, surgical stage, tumor grade, American Society of Anesthesiologists class, preoperative serum CA-125 and platelet levels, percentage with or amount of ascites, size or location of largest tumor mass, or type of postoperative chemotherapy. Patients in Group 2 vs Group 1 more frequently had extensive upper abdominal procedure(s) (38% vs 0%, respectively; $P<0.001$) and cytoreduction to residual disease <1 cm (80% vs 46%, respectively; $P<0.01$). Five-year PFS and OS rates were significantly improved in Group 2. For Group 2 vs Group 1 patients, 5-year PFS rates were 31% vs 14%, respectively (hazard ratio, 0.757; 95% CI, 0.601–0.953;$P=0.01$]; and 5-year OS rates were 47% vs 35%, respectively (HR, 0.764; 95% CI, 0.592–0.987;$P=0.03$].

Conclusion. The incorporation of extensive upper abdominal procedures resulted in increased optimal cytoreduction rates and significantly improved PFS and OS. A paradigm shift toward more complete primary cytoreduction can improve survival for patients with advanced ovarian, tubal, and peritoneal carcinomas.

Introduction

Of the estimated 25,000 American women diagnosed each year with primary ovarian, fallopian tube, or peritoneal carcinoma, the majority present with advanced-stage disease [1]. For these patients, standard initial therapy consists of cytoreductive surgery followed by a combination of taxane and platinum-based chemotherapy [2,3]. Numerous studies have demonstrated a survival advantage for patients who undergo "optimal" vs "suboptimal" primary surgical cytoreduction or "debulking" [4–7].

The percentage of patients who undergo optimal cytoreduction for advanced disease varies widely in the literature from 15% to 85% [7]. Reports of optimal cytoreduction rates > 50% generally included a substantial number of patients who underwent extensive upper abdominal procedures to attain optimal residual status [8–10]. Historically, the rate of optimal primary cytoreduction for patients with advanced disease at our institution has been less than 50% [4,11,12]. In these series, extensive upper abdominal resections were not part of the surgical armamentarium of advanced-disease management. Consequently, large-volume upper abdominal tumor involving the diaphragm, liver, and/or spleen was deemed "unresectable", and the patient was left with suboptimal residual disease.

In an attempt to improve our optimal cytoreductive rates, in January 2001, we expanded our surgical efforts by incorporating extensive upper abdominal surgery into the primary cytoreductive effort. The modified approach included diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver

☆ Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology in Chicago, IL. June 1–5, 2007.

* Corresponding author. 1275 York Ave Gynecology Service, Department of Surgery Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065, USA.
E-mail address: gynbreast@mskcc.org (D.S. Chi).

0090-8258/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2009.03.018

resection, cholecystectomy and resection of tumor from the porta hepatis in cases where the primary surgeon deemed them necessary to achieve optimal cytoreduction. This paradigm shift led to an increased rate of optimal primary cytoreduction without increasing the rates of major complications or length of hospital stay [13]. This current study was designed to determine the impact of the incorporation of extensive upper abdominal procedures on progression-free survival (PFS) and overall survival (OS) in advanced ovarian, fallopian tube, and primary peritoneal carcinoma.

Patients and methods

Eligibility

After obtaining Institutional Review Board approval, we used our prospectively maintained Virginia K. Pierce Gynecology Service Database to identify all patients with stage IIIC and IV ovarian, fallopian tube, and peritoneal carcinoma who underwent primary cytoreduction at our institution between 1/1/96 and 12/31/04. All surgery was done by an attending gynecologic oncologist. Due to their rarity, unique management approach, and relatively poor prognosis, mucinous and carcinosarcoma histologies were excluded. Patients with non-epithelial cancers, low malignant potential tumors, and those who received neoadjuvant chemotherapy were also excluded.

Study groups

Eligible patients were classified into two groups based on the date of surgery. Group 1, the control group, consisted of all 168 patients who underwent primary cytoreduction during the 4-year period from 1/1/96 to 12/31/99. During this period, our cytoreductive approach did not include extensive upper abdominal procedures.

Group 2, the study group, consisted of all 210 patients who underwent primary debulking surgery during the 4-year period from 1/1/01 to 12/31/04. This latter period encompassed the time when we changed our surgical paradigm to incorporate extensive upper abdominal procedures but had not yet begun to give primary intraperitoneal chemotherapy.

Extensive upper abdominal procedures were defined as diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and resection of tumor from the porta hepatis performed only as necessary to achieve optimal cytoreduction. Patients operated on from January 2000 to December 2000 were not included in the study as some surgeons were employing extensive upper abdominal surgery during this time, but the paradigm had not changed for the entire service.

Data collection and statistical analysis

Individual records for all patients were reviewed, and demographic, clinical, surgical, pathologic, and follow-up data were extracted. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [14]. During the first time period (1996–1999), tumor histology and grade of differentiation were assigned by World Health Organization (WHO) criteria for typing of ovarian neoplasms [15]. However, during the latter time period (2001–2004), our subclassification of ovarian carcinomas changed, and tumor histology was assigned based on this modified system [16].

Optimal cytoreduction was defined as no residual tumor nodule measuring greater than 1 cm in maximal dimension at the end of the surgical procedure. Pelvic and or para-aortic lymphadenectomies were performed at the discretion of the primary surgeon if it was felt that it would aid in the cytoreductive outcome. All perioperative complications at our institution were graded according to a published classification system [13]. Perioperative complications and death were defined as any adverse events related to the operative treatment occurring within 30 days of surgery. For patients who had more than one complication, the highest grade complication was used in the analysis.

Categorical variables were compared using the Fisher exact test, and continuous variables were compared using the Student's *t* test. All statistical tests were two-sided, and differences were considered significant at a level of $P<0.05$. Date of progression was determined by computed tomography (CT) scan and/or CA-125 levels. When determined by CT scan, the date of progression was taken as the first appearance of one or more new lesions or increased size of existing lesions. When determined by CA-125 level, date of progression was defined as the first date of the initial CA-125 of greater than or equal to two times the nadir value or upper limit of normal, as applicable [17,18]. When a subsequent CT scan confirmed that the rise in CA-125 indicated progression, the date of progression was defined as the date of CA-125 rise. PFS was defined as the time interval from date of surgery to the date of the documented first recurrence or progression of disease. If there was no documented recurrence, PFS was calculated from the date of surgery to the date of last follow-up or death, whichever occurred first. OS was defined as the time interval from date of surgery to the date of death or last follow-up. The Kaplan–Meier method was used to estimate survival curves and differences in survival were analyzed utilizing the log–rank test [19,20].

Results

The median age of the 378 patient study cohort was 61 years. Most patients had stage IIIC, grade 3, serous ovarian cancer. There were no statistically significant differences between the two groups in median age, primary disease site, tumor stage, tumor grade,

Table 1
Patient and tumor characteristics.

Variable	Group 1 ($n=168$)	Group 2 ($n=210$)	*P* value
Median age (range)	60 yrs (25–85)	61 yrs (25–95)	NS
Primary site of disease			
Ovary	149 (89%)	181 (86%)	NS
Peritoneum	14 (8%)	21 (10%)	
Fallopian tube	5 (3%)	8 (4%)	
Stage of disease			
IIIC	147 (88%)	174 (83%)	NS
IV	21 (12%)	36 (17%)	
Tumor grade			
1	3 (2%)	7 (3%)	NS
2	35 (21%)	23 (11%)	
3	121 (72%)	164 (78%)	
N/A	9 (5%)	16 (8%)	
Histologic type			
Serous	102 (61%)	181 (86%)	<0.001
Endometrioid	32 (19%)	0 (0%)	
Clear cell	11 (7%)	0 (0%)	
Mixed	15 (9%)	16 (8%)	
Other	8 (5%)	13 (6%)	
Median preoperative CA-125 (range)	870 U/mL (7–16,200)	837 U/mL (18–20,888)	NS
Median preoperative platelet count (range)	371 K/μL (128–243)	368 K/μL (113–788)	NS
ASA class			
I	13 (8%)	17 (8%)	NS
II	104 (62%)	119 (57%)	
III	31 (18%)	69 (33%)	
N/A	20 (12%)	5 (2%)	

NS, not significant; ASA, American Society of Anesthesiologists; N/A, not available.

Table 2
Operative findings.

Variable	Group 1 ($n=168$)	Group 2 ($n=210$)	P value
Location of largest mass			
Pelvis	66 (39%)	76 (36%)	NS
Omentum	85 (51%)	113 (54%)	
Upper abdomen	6 (4%)	8 (4%)	
Other	11 (6%)	13 (6%)	
Size of largest mass (cm)			
≤5 cm	22 (13%)	21 (10%)	NS
5.1–10 cm	35 (21%)	46 (22%)	
10.1–15 cm	43 (26%)	32 (15%)	
15.1–20 cm	29 (17%)	42 (20%)	
>20 cm	30 (18%)	65 (31%)	
Ascites (mL)			
None	31 (18%)	33 (16%)	NS
1–500	39 (23%)	15 (7%)	
501–1000	19 (11%)	55 (26%)	
1001–2000	14 (8%)	33 (16%)	
2001–5000	30 (18%)	33 (16%)	
>5000	17 (10%)	15 (7%)	
N/A	18 (11%)	55 (26%)	

NS, not significant; N/A, not available.

preoperative CA-125 levels, preoperative platelet counts, or American Society of Anesthesiologists class (Table 1). Based on the modified histologic classification system used in the Group 2 patients, there was a significant difference between the two groups in the percentage of patients with serous vs non-serous histology. However, the changes in histologic classification did not have any clinical impact as histologic type was not a significant prognostic factor on univariate analysis of Group 1 patients, Group 2 patients, or the entire study cohort (analysis not shown).

Intraoperative findings were similar between the two groups with regard to the location of the largest mass identified, size of the largest mass, the percentage of patients with ascites, and the volume of ascites reported (Table 2). The majority of patients underwent multiple cytoreductive procedures (Table 3). Two patients in Group 1, not listed in Tables 3 and 4, had cholecystectomies for cholelithiasis and not for cytoreductive purposes. None of the other extensive upper abdominal procedures were performed on any Group 1 patients compared to 38% of patients in Group 2 ($P<0.001$).

The rate of optimal cytoreduction significantly increased from 46% (78/168) in Group 1 patients to 80% (167/210) in Group 2 patients ($P<0.01$) (Table 4). The percentage of patients left with no grossly visible or palpable disease also increased from 11% in Group 1 to 27% in Group 2. Estimated blood loss was significantly higher for the second group of patients, as was the operative time and the percentage of patients requiring intraoperative blood transfusions. The rate of major perioperative complications was significantly greater in Group 2 patients, with higher rates of infectious, gastrointestinal, and hematologic morbidity. However, perioperative mortality was similar (1 [0.6%] in Group 1 patients vs 2 [1%] in Group 2 patients).

Table 3
Cytoreductive procedures performed.

Procedures performed	Group 1 ($n=168$)	Group 2 ($n=210$)
Standard		
Hysterectomy	129 (77%)	183 (87%)
USO/BSO	153 (91%)	184 (88%)
Omentectomy	135 (80%)	182 (87%)
Small bowel resection	6 (4%)	8 (4%)
Large bowel resection	10 (6%)	73 (35%)
Appendectomy	17 (10%)	37 (18%)
Pelvic lymph node dissection	11 (7%)	59 (28%)
Para-aortic lymph node dissection	11 (7%)	47 (22%)
Extensive upper abdominal		
Diaphragm peritonectomy/resection	0 (0%)	73 (35%)
Splenectomy	0 (0%)	26 (12%)
Distal pancreatectomy	0 (0%)	9 (4%)
Liver resection	0 (0%)	13 (6%)
Resection porta hepatis tumor	0 (0%)	11 (5%)
Cholecystectomy	0 (0%)	10 (5%)

USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy.

Table 4
Surgical outcomes.

Variable	Group 1 ($n=168$)	Group 2 ($n=210$)	P value
Extensive upper abdominal procedure	0 (0%)	79 (38%)	<0.001
Upper Abdominal Procedure(s)			
Residual disease	19 (11%)	57 (27%)	<0.001
None grossly visible			
0.1–1 cm	59 (35%)	110 (52%)	
>1 cm	90 (54%)	43 (20%)	
Estimated blood loss (L)			
<1	142 (85%)	136 (65%)	<0.001
1–2	16 (10%)	43 (20%)	
2–3	3 (2%)	13 (6%)	
>3	1 (1%)	6 (3%)	
N/A	6 (4%)	12 (6%)	
Intraoperative units blood transfused	Units Blood Transfused		
None	134 (80%)	124 (59%)	<0.001
1–2	20 (12%)	44 (21%)	
3–4	6 (3%)	25 (12%)	
≥5	0 (0%)	12 (6%)	
N/A	8 (5%)	5 (2%)	
Operative time (minutes)			
≤120	38 (23%)	15 (7%)	<0.001
120–240	86 (51%)	86 (41%)	
241–360	20 (12%)	63 (30%)	
>360	5 (3%)	45 (21%)	
N/A	19 (11%)	1 (1%)	
Major complications			
Infectious	7 (4%)	21 (10%)	0.015
Gastrointestinal	3 (2%)	8 (4%)	
Hematologic	0 (0%)	5 (2%)	
Cardiopulmonary	1 (0.6%)	4 (2%)	
Thromboembolic	3 (2%)	3 (1%)	
Systemic taxane–platinum chemotherapy	Taxane-Platinum Chemotherapy		
Initiated therapy			NS
Completed ≥5 cycles	141 (84%)	184 (88%)	NS
Intraperitoneal chemotherapy after second-look surgery	70 (42%)	77 (37%)	NS

N/A, not available; NS, not significant.

During the entire 9-year study period, our intent was to treat all patients after primary surgery with 5–6 cycles of systemic taxane and platinum-based chemotherapy. A similar percentage of patients in both groups initiated and were able to complete 5 or more cycles of taxane and platinum-based systemic chemotherapy (Table 4). In both groups, patients were recorded as not having received 5 or more cycles of this regimen due to the following: patient refusal, incomplete chemotherapy records, change in regimen due to progression of disease, and death prior to or during therapy. As previously reported, those patients in a complete clinical remission were offered second-look surgery and further cisplatin-based intraperitoneal chemotherapy if no or minimal disease was found at second look [21]. A similar percentage of patients in each group received intraperitoneal chemotherapy after second-look surgery (Table 4).

Median follow-up for surviving patients was 60 months for the entire cohort, 92 months for Group 1, and 54 months for Group 2. Five-year PFS and OS rates were significantly improved in the latter group in which extensive upper abdominal procedures were utilized as necessary. The 5-year PFS rates for Group 2 vs Group 1 patients were 31% vs 14%, respectively (hazard ratio [HR], 0.757; 95% CI, 0.601–0.953; $P=0.01$) (Fig. 1A). Five-year OS rates for Group 2 vs Group 1 patients were 47% vs 35%, respectively (HR, 0.764; 95% CI, 0.592–0.987; $P=0.03$) (Fig. 1B). The median OS for Group 2 patients was

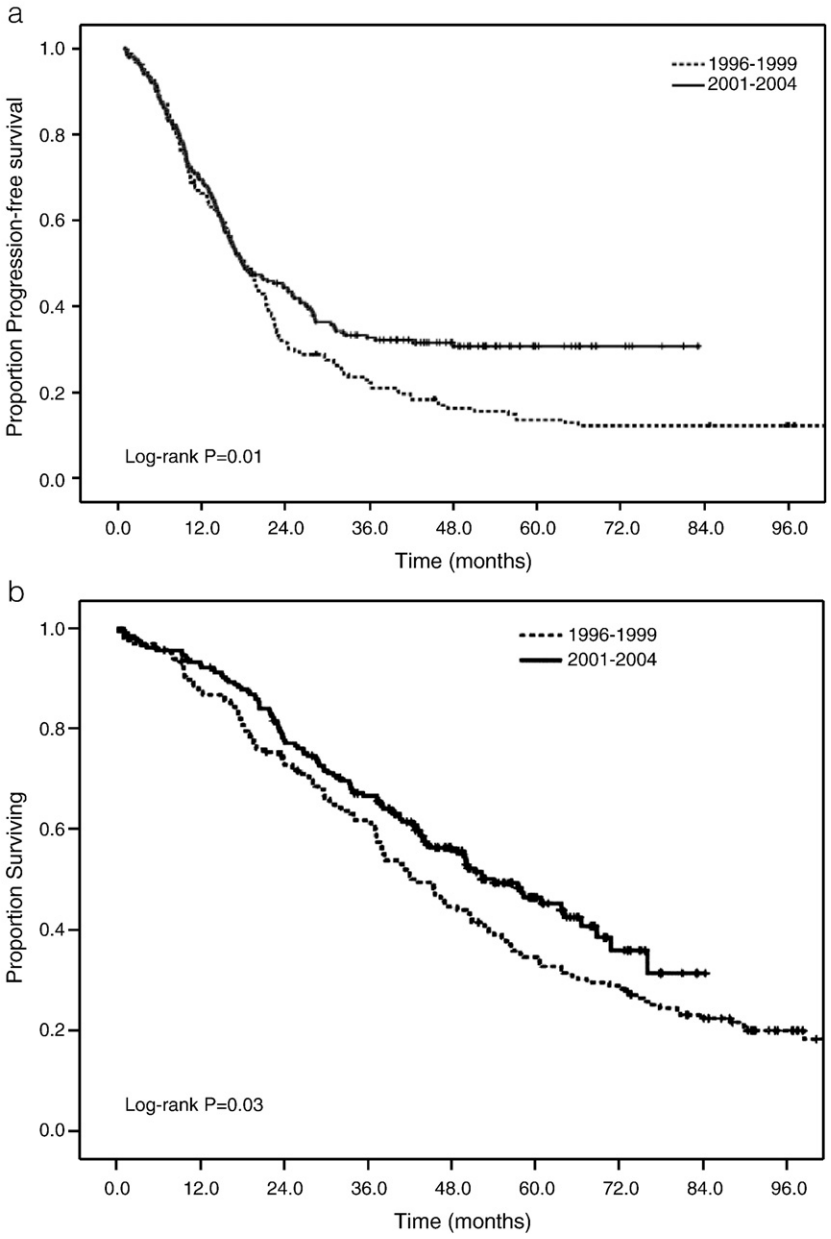

Fig. 1. (A) Progression-free survival, 1996–1999 vs 2001–2004. (B) Overall survival, 1996–1999 vs 2001–2004.

54 months, which was significantly longer than the 43 month median OS for Group 1 patients ($P = 0.03$).

Discussion

Since the seminal work by Griffiths in 1975, numerous studies have demonstrated the important prognostic significance of optimal cytoreduction and minimal residual disease for advanced ovarian carcinoma [4,7,22]. In the 1990s, Hoskins and the Gynecologic Oncology Group (GOG) showed that suboptimal debulking, regardless of the diameter of the residual disease, offered no survival benefit [23]. They reported that patients with stage III ovarian carcinoma with <2 cm residual disease had a significant improvement in survival over those patients left with >2 cm residual disease. However, there were only 31 patients with residual disease between 1 and 2 cm in these GOG studies.

We subsequently analyzed prognostic factors in 282 patients with advanced ovarian carcinoma who had primary surgery at our institution between 1987 and 1994. Only patient age, the presence or absence of ascites, and size of residual disease were significant prognostic factors [4]. We found no survival benefit to cytoreduction unless <1 cm residual disease could be attained. Unfortunately, during this early time period, cytoreduction to this level of residual disease was not the goal of every surgeon as some felt that a 2 cm cutoff was sufficient [11,12]. Therefore, cytoreduction to <1 cm residual disease was only attained in 25% of patients, with a median OS of 34 months for the entire 282 patient cohort.

The concept of optimal cytoreduction rates and corresponding survival outcomes was best illustrated in a meta-analysis by Bristow et al. who analyzed the median survival of patient study cohorts as a function of "maximal" or optimal cytoreduction rates [7]. They evaluated 81 studies including 6995 patients with advanced ovarian cancer treated during the platinum-based chemotherapy era. Their analysis led to the development of a theoretical model that suggested that each 10% increase in maximum or optimal cytoreduction rate prolonged median cohort survival by 5.5%. More specifically, when actuarial survival was estimated, centers with optimal cytoreduction rates of <25% had a mean weighted median survival time of

23 months, whereas cohorts with optimal cytoreduction rates of >75% had a mean weighted median survival time of 34 months, an increase of 50%.

In an attempt to improve our optimal cytoreduction rates, we initially increased the radicality of our pelvic resections to include removal of the rectosigmoid either separately or en bloc with the uterus and adnexa [24]. However, numerous studies have shown that optimal cytoreduction rates greater than 50% often require the incorporation of a variety of extensive upper abdominal surgical procedures [8–10]. Consequently, in 2001 our service instituted a paradigm change by incorporating the use of extensive upper abdominal surgery into our cytoreductive approach for advanced ovarian, fallopian tube, and primary peritoneal carcinoma [13]. This led to a significant improvement in our optimal cytoreduction rates.

However, the question that had remained unanswered was whether or not the increased optimal cytoreduction rates truly translated into improved survival, as predicted by the Bristow model. This question was partially answered in an analysis of our data performed by Eisenhauer et al. [25] In this study of all patients with stage IIIC and IV ovarian carcinoma who had primary surgery at our institution between 1998 and 2003, those patients who were optimally cytoreduced with the utilization of extensive upper abdominal surgery had improved survival compared to those who had suboptimal cytoreduction. Moreover, the PFS and OS of those patients who needed extensive upper abdominal procedures was identical to that of those who had less tumor volume and were able to be optimally cytoreduced with less-extensive surgery.

Critics of our approach include those who may suggest that the improved outcomes of those patients who underwent extensive upper abdominal surgery in the study by Eisenhauer et al. were merely a function of "good tumor biology" in those patients, as opposed to good surgical technique, which resulted in the ability to optimally cytoreduce these patients [26,27]. To address the possibility of this "Will Rogers" phenomenon of shifting patients from one group to another without actually improving OS, we waited until we were able to get long enough follow-up to do the present study. Since we changed our chemotherapy approach in January 2005 to incorporate intraperitoneal therapy into the primary regimen, we set our study group period for that after the change in surgical paradigm in January 2001 until just before the change in chemotherapy paradigm in January 2005. Given that the study period for the extensive surgery group was a full 4 years, we then chose the control group to be the immediate 4 years prior to our conversion to the new surgical paradigm.

We feel that the study design was effective in that almost all preoperative and intraoperative prognostic factors were similar between the two groups. The only significant difference between the two groups in these areas was in the histologic tumor subtypes. As explained in the Methods section, however, we changed the criteria for certain histologic classifications after 2001, and this accounts for the difference rather than a change in patient referrals or selection for surgery.

Our study does demonstrate that a more extensive surgical approach is associated with longer operative times, increased blood loss and transfusions, as well as higher morbidity. Mortality is not increased, however, and most importantly, the change in surgical paradigm while utilizing identical chemotherapeutic regimens translated into a significant improvement in PFS and OS. We feel these results support the principle set forth in the meta-analysis by Bristow et al. [7]. Fig. 2 demonstrates the improvement in overall survival for patients with advanced ovarian cancer at our institution from 1987 to 2004. During those 18 years, primary management and chemotherapy have been essentially the same except for the change in our surgical approach as outlined in this study and the fact that many of the patients treated between 1987 and 1994 did not receive paclitaxel as part of their primary chemotherapy regimen[4]. However, most did receive paclitaxel subsequent to their primary platinum-based chemotherapy so based on the GOG study reported by Muggia et al., it is unclear if the overall survival for this early cohort would have been significantly improved if paclitaxel had been included in the primary regimen of all the patients during this early time period [28]. Nevertheless, the most likely reason for the difference in the survival curve from our center compared to the curve from the Bristow meta-analysis in Fig. 2 is that the meta-analysis included all studies that used platinum-based chemotherapy, with many not utilizing taxanes at all, whereas taxane and platinum-based chemotherapy has been utilized at institution for most of the past 2 decades.

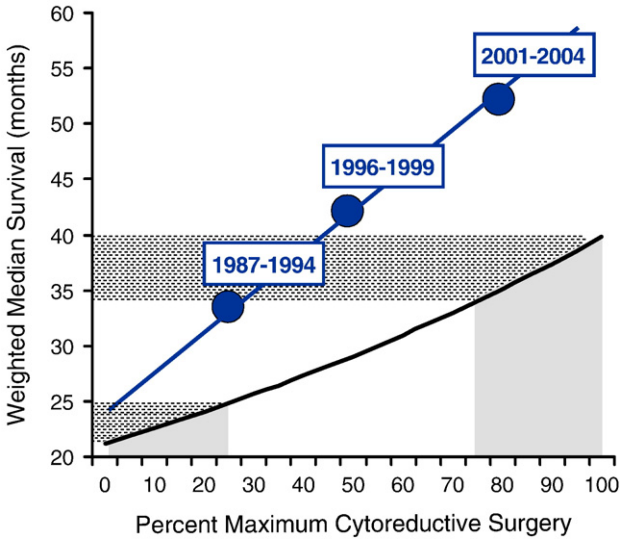

Fig. 2. Median overall survival as a function of percent maximum or optimal cytoreductive surgery. MSKCC survival 1987–2004 superimposed on model by Bristow et al. (Modified with permission Bristow RE, Tomacruz RS, Armstrong DK, et al: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20:1248–1259, 2002).

The change in our management paradigm toward a more aggressive surgical approach is essentially the opposite to the change made by Vergote et al. [29]. Pointing to an especially high complication rate and 6% mortality rate in patients undergoing primary cytoreduction from 1980 to 1988, they changed their approach to incorporate primary or "neoadjuvant" chemotherapy in 43% of patients treated in the latter time period of 1989–1997. They reported a statistically significant improvement in OS for the latter group. However, the two groups received significantly different chemotherapy regimens. No patient in the earlier primary cytoreductive cohort received combination taxane and platinum-based therapy, 5% were treated with radiation therapy, and 19% received no treatment at all. In the latter cohort, 20% of patients received combination taxane and platinum-based chemotherapy and 3% of patients received no treatment. Furthermore, median OS for both groups was less than 36 months, which is inferior to contemporary studies [2,3,5].

While studies such as this one by Vergote et al. and others do demonstrate decreased morbidity with neoadjuvant chemotherapy, none of the studies advocating this approach have reported the prolonged median survivals of more than 60 months that have been consistently reported in patient cohorts undergoing primary optimal cytoreduction [2,3,6]. A recent meta-analysis of all neoadjuvant chemotherapy studies from 1989 to 2005 suggested that there may be an inverse relationship between the number of cycles of neoadjuvant chemotherapy and OS [30].

The strengths of our study are the homogeneity of the patient populations studied and the consistent management approaches separated only by time period and differing only in surgical approach. The weaknesses are that the study is retrospective and

the management approaches after primary therapy were not controlled. However, even in prospective phase III primary chemotherapy trials, the management after primary therapy is not controlled [2,3]. Furthermore, our management approaches regarding consolidation therapy, persistent disease, and tumor relapse did not undergo significant change during the study period, so it is unlikely that the management after primary therapy had any impact on the different survival outcomes between the two groups [21,31–33]. While one could make the argument that better salvage chemotherapy was available and used in the more recent time period, the improved PFS refutes this notion and supports the premise that the 11 month improvement in median OS was a result of the change in surgical paradigm and not any other factor.

In summary, this study demonstrates that the incorporation of extensive upper abdominal surgery into the operative strategy can lead to a significant increase in optimal cytoreduction rates and consequent improved PFS and OS for advanced ovarian, tubal, and peritoneal carcinoma. We feel that the significant improvement in PFS and OS seen in our study justifies the recommendation that surgeons operating in this setting should consider using these upper abdominal procedures when necessary or have a surgical consultant available who is trained to do these procedures as indicated. Furthermore, minimizing intraperitoneal disease is critical for optimizing outcomes given the findings of GOG 172 and the subsequent recommendation by the National Cancer Institute to consider primary intraperitoneal chemotherapy as standard therapy for those patients who have ≤ 1 cm residual disease [3,34].

Conflict of interest statement

1. Dennis S. Chi, MD: Genzyme — Speaker's Bureau.
2. Eric L. Eisenhauer, MD: no conflicts of interest to declare.
3. Oliver Zivanovic, MD: no conflicts of interest to declare.
4. Yukio Sonoda, MD: Genzyme — speaker; Plasma Surgical — research support.
5. Nadeem R. Abu-Rustum, MD: no conflicts of interest to declare.
6. Douglas A. Levine, MD: no conflicts of interest to declare.
7. Matthew W. Guile, MD: no conflicts of interest to declare.
8. Robert E. Bristow, MD: no conflicts of interest to declare.
9. Carol Aghajanian, MD: no conflicts of interest to declare.
10. Richard R. Barakat, MD: no conflicts of interest to declare.

References

[1] Jemal A, Siegel R, Ward E Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
[2] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al, Gynecologic Oncology Group.. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194–200.
[3] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al, Gynecologic Oncology Group.. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
[4] Chi DS, Liao JB, Leon LF, Venkatraman ES, Hensley ML, Bhaskaran D, et al. Identification of prognostic factors in advanced ovarian epithelial carcinoma. Gynecol Oncol 2001;82:532–7.
[5] Winter 3rd WE, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, et al, Gynecologic Oncology Group.. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2007;25:3621–7.
[6] Chi DS, Eisenhauer EL, Lang J, Huh J, Haddad L, Abu-Rustum NR, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma? Gynecol Oncol 2006;103:559–64.
[7] Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248–59.
[8] Kuhn W, Glorack G, Roder J, Schmalfeldt B, Pache L, Rust M, et al. The influence of upper abdominal surgery on perioperative morbidity and mortality in patients with advanced ovarian cancer FIGO III and IV. Int J Gynecol Cancer 1998;8:56–63.
[9] Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol 2003;90:390–6.
[10] Aletti GD, Dowdy SC, Gostout BS, Jones MB, Stanhope CR, Wilson TO, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 2006;107:77–85.
[11] Redman JR, Petroni GR, Saigo PE, Geller NL, Hakes TB. Prognostic factors in advanced ovarian carcinoma. J Clin Oncol 1986;4:515–23.
[12] Curtin JP, Malik R, Venkatraman ES, Barakat RR, Hoskins WJ. Stage IV ovarian cancer: impact of surgical debulking. Gynecol Oncol 1997;64:9–12.
[13] Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol 2004;94:650–4.
[14] Staging Announcement. FIGO Cancer Committee. Gynecol Oncol 1986;25:383–5.
[15] Serov SF, Scully RE, Sobin LH. Histologic typing of ovarian tumors. International histologic classification of tumors, 17. Geneva: World Health Organization; 1973.
[16] Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. Int J Gynecol Path 2008;27:161–74.
[17] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[18] Rustin GJ, Marples M, Nelstrop AE, Mahmoudi M, Meyer T. Use of CA-125 to define progression of ovarian cancer in patients with persistently elevated levels. J Clin Oncol 2001;19:4054–7.
[19] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
[20] Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–70.
[21] Barakat RR, Sabbatini P, Bhaskaran D, Revzin M, Smith A, Venkatraman E, et al. Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. J Clin Oncol 2002;20:694–8.
[22] Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975;42:101–4.
[23] Hoskins WJ. Epithelial ovarian carcinoma: principles of primary surgery. Gynecol Oncol 1994;55:S91–6.
[24] Mourton SM, Temple LK, Abu-Rustum NR, Gemignani ML, Sonoda Y, Bochner BH, et al. Morbidity of rectosigmoid resection and anastomosis in high risk patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol 2005;99:608–14.
[25] Eisenhauer EL, Abu-Rustum N, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC–IV epithelial ovarian cancer. Gynecol Oncol 2006;103:1083–90.
[26] Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 trial. J Clin Oncol 2005;23:8802–11.
[27] Markman M. Concept of optimal surgical cytoreduction in advanced ovarian cancer: a brief critique and a call for action. J Clin Oncol 2007;25:4168–70.
[28] Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz SL, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2000;18:106–15.
[29] Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71:431–6.
[30] Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol 2006;103:1070–6.
[31] Dizon DS, Hensley ML, Poynor EA, Sabbatini P, Aghajanian C, Hummer A, et al. Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer. J Clin Oncol 2002;20:1238–47.
[32] McCreath WA, Abu-Rustum NR, Venkatraman ES, Venkatraman ES, Caceres A, Bier R, et al. Identification of prognostic factors after positive second look surgery in epithelial ovarian carcinoma. Gynecol Oncol 2006;102:8–14.
[33] Chi DS, McCaughty K, Schwabenbauer S, Huh J, Schwabenbauer S, Hummer AJ, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent platinum sensitive epithelial ovarian carcinoma. Cancer 2006;106:1933–9.
[34] National Cancer Institute. Clinical Announcement: Intraperitoneal chemotherapy for ovarian cancer. 2006. http://ctep.cancer.gov/highlights/clin_annc_010506.pdf.