Gynecologic Oncology 130 (2013) 493–498

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

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

Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis

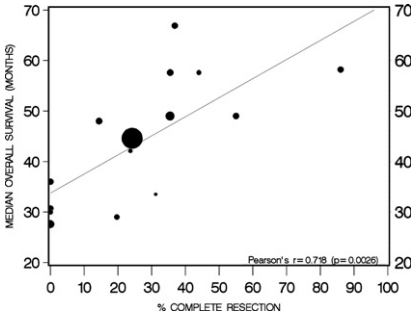
Suk-Joon Chang [a], Melissa Hodeib [b], Jenny Chang [c], Robert E. Bristow [b,*]

[a] Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Republic of Korea
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California, Irvine School of Medicine, Orange, CA, USA
[c] Department of Epidemiology, University of California, Irvine, Irvine, CA, USA

HIGHLIGHTS

- The proportion of patients left with no gross residual disease is independently predictive of survival.
- The proportion of patients receiving intraperitoneal chemotherapy is a significant predictor of cohort survival time.
- These data underscore the synergy between regional therapeutic efficacy and the completeness of surgical resection.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 April 2013
Accepted 30 May 2013
Available online 6 June 2013

Keywords:
Advanced ovarian cancer
Complete cytoreduction
Residual disease

ABSTRACT

Objective. To quantify the impact of complete cytoreduction to no gross residual disease on overall survival among patients with advanced-stage ovarian cancer treated during the platinum–taxane era.

Methods. PubMed and Cochrane Library databases were searched for all articles on primary cytoreductive surgery for advanced-stage ovarian cancer published from 1/1996 to 7/2011. A total of 18 relevant studies (13,257 patients) were identified for analysis. Simple and multiple linear regression analyses, with weighted correlation calculations, were used to assess the effect on median survival time of clinical and treatment-related factors.

Results. The mean weighted median overall survival time for all cohorts was 44.4 months (range, 27.6–66.9 months). Simple linear regression analysis revealed that residual disease, stage IV disease, and use of intraperitoneal chemotherapy were significantly associated with median survival time. After controlling for other factors on multiple linear regression analysis, each 10% increase in the proportion of patients undergoing complete cytoreduction to no gross residual disease was associated with a significant and independent 2.3-month increase (95%CI = 0.6–4.0, p = 0.011) in cohort median survival compared to a 1.8-month increase (95%CI = 0.6–3.0, p = 0.004) in cohort median survival for optimal cytoreduction (residual disease ≤ 1 cm). Each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was associated with a significant and independent 3.9-month increase (95%CI = 1.1–6.8, p = 0.008) in median cohort survival time.

Conclusions. For advanced-stage ovarian cancer treated during the platinum–taxane era, the proportions of patients left with no gross residual disease and receiving intraperitoneal chemotherapy are independently significant factors associated with the most favorable cohort survival time.

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California, Irvine School of Medicine, 101 The City Drive, Building 56, Room 260, Orange, CA 92868, USA. Fax: +1 714 456 6632.
E-mail address: rbristow@uci.edu (R.E. Bristow).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.05.040

Introduction

Worldwide, approximately 225,000 women are diagnosed with ovarian cancer and 140,000 women die from this disease annually [1]. In the United States, ovarian cancer remains the leading cause of death from gynecological malignancy, with 21,990 new cases and 15,460 deaths in 2011 [1]. The majority of ovarian cancer patients are initially diagnosed with tumor metastases beyond the ovary, which results in diminished chances of long-term survival [2]. Surgical cytoreduction and adjuvant chemotherapy are the cornerstones of management for advanced ovarian cancer. Since the mid-1990s, primary cytoreductive surgery followed by platinum and taxane-based combination chemotherapy has been the standard treatment regimen for advanced-stage disease [3–6].

Residual disease after cytoreductive surgery for advanced-stage ovarian cancer is estimated as the largest diameter of remaining tumor and is one of the most important prognostic factors [7,8]. Paradoxically, universal consensus regarding the definition of "optimal" residual disease has been lacking. The Gynecologic Oncology Group (GOG) has defined optimal residual disease as residual tumor ≤ 1 cm in the largest diameter [9,10]. However, optimal residual disease has been variously defined as ranging from no gross residual disease to remaining tumor nodules measuring ≤ 2 cm [11–14]. More contemporary data suggest that the most favorable survival outcomes are associated with complete cytoreduction to no gross residual disease [15–22]. Despite this observation the relative impact of complete cytoreduction, as opposed to "optimal but visible residual disease", within the context of contemporary platinum–taxane-based adjuvant therapy has been difficult to determine. Therefore, the objective of the current study was to quantify the impact of complete cytoreduction to no gross residual disease on overall survival among patients with advanced-stage ovarian cancer treated during the platinum–taxane era using the technique of meta-analysis.

Methods

Study selection and data extraction

Potential articles for analysis were identified from a literature search of the National Library of Medicine (PubMed) and the Cochrane Library for all English-language publications between January 1, 1996 and July 31, 2011. The keywords used were "ovarian neoplasm," "ovarian carcinoma," "ovarian cancer," and "surgery." Two authors (S.J.C. and R.E.B.) independently reviewed the titles and abstracts of publications searched, and excluded the unrelated articles. A full-text audit of identified articles was performed, and publications that fulfilled selection criteria were included in the study.

Study inclusion criteria for meta-analysis were as follows: 1) primary epithelial ovarian, fallopian tube, or peritoneal carcinoma; 2) International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV disease; 3) primary cytoreductive surgery; 4) adjuvant chemotherapy administered when both taxane and platinum agents were available; 5) residual disease reported using the criteria of no gross (microscopic) residual disease, residual disease 0–1.0 cm, residual disease of 0.1–1.0 cm, or residual disease > 1 cm; and 6) survival analysis according to the aforementioned residual disease criteria. Optimal residual disease was defined as residual tumor size ≤ 1.0 cm in the largest diameter based on the GOG criteria. In cases of multiple publications with overlapping cohort data, the most relevant study satisfying the above criteria was selected for analysis. In the case of ancillary studies analyzing previously published data, only the original study was included for meta-analysis. For each eligible study cohort the following information was recorded: study design (randomized controlled trial, prospective trial, retrospective review), year of publication, the temporal midpoint of study accrual time period, number of study subjects, median patient age at diagnosis, the proportion of patients with stage IV disease, the proportion of patients receiving taxane chemotherapy, the proportion of patients receiving intraperitoneal chemotherapy, the proportion of patients completing a planned 6-cycles of chemotherapy, the proportion of patients undergoing complete cytoreduction to no gross residual disease, the proportion of patients left with optimal (≤1 cm) residual disease, and the reported median overall survival time.

Statistical analysis

Simple linear regression models were generated to examine the effect on median cohort survival time of the predictor variables. Each regression model was weighted by the number of patients in each cohort. Multiple linear regression analyses were used to derive the independent effects of the aforementioned variables on log median survival time, using an imputed dataset to account for missing values, simultaneously controlling for other measured variables that could potentially affect survival. Because the surgical outcome criteria of no gross residual and optimal residual disease are not mutually exclusive, separate multiple linear regression analyses were performed using no gross residual disease (model 1) or optimal residual disease (model 2) as the surgical outcome criteria. All results reflect a two-sided p-value, and a p-value < 0.05 was considered statistically significant. All analyses were carried out using SAS 9.2 statistical software package.

Results

Study characteristics

The initial electronic search yielded 1203 articles. The full-length published reports of 104 studies were formally reviewed, and 15 studies were identified as containing the minimum study inclusion criteria [5,15–21,23–29]. Of these 15 studies, 4 studies [18–21] were ancillary data studies which retrospectively reanalyzed the data collected for 9 previous randomized prospective trials [5,6,23,30–35], and these ancillary data studies included overlapping data with two other studies [5,23]. Therefore, the original randomized trials were included in the meta-analysis instead of the 4 ancillary data studies. Ultimately, 18 studies were selected for inclusion in the meta-analysis (Table 1) [3,5,6,15–17,23–35]. Seventeen studies were published after 2000 and one study was published in 1996. Six studies were retrospective observational series from single institution and 12 studies were randomized controlled trials investigating the efficacy of adjuvant chemotherapy regimens.

The clinical characteristics of the final study population cohorts (13,257 patients) are summarized in Table 1. There were no missing values for the predictor variables of study accrual time period midpoint, median cohort age at diagnosis, proportion of patients receiving intraperitoneal chemotherapy, and proportion of patients undergoing optimal cytoreductive surgery. For the remaining predictor variables, the percentage of all patients with missing values was 11.1% for receipt of 6 cycles of chemotherapy, 16.7% for complete cytoreduction, and 27.8% for proportion receiving taxane chemotherapy.

The mean weighted median overall survival time for all cohorts was 44.4 months (range, 27.6–66.9 months), and the median age was 59 years (range, 56–64 years). The mean weighted proportion of patients in each cohort with residual disease ≤ 1 cm in maximal diameter was 62.3% (range, 0%–100%). The mean weighted proportion of patients in each cohort undergoing complete cytoreduction was 25.9% (range, 0%–86.0%). All cohorts received platinum-based chemotherapy, and the weighted mean proportion of patients in each cohort receiving taxane chemotherapy was 65.9% (range, 20.0%–100%). Two randomized prospective trials on intravenous versus intraperitoneal chemotherapy were included, and there were 440 patients receiving intraperitoneal chemotherapy.

Table 1
Study characteristics.

Reference	Year	Median age (years)	N	Percent stage IV disease	Percent taxane therapy	Percent IP therapy	Percent 6 cycles of therapy	Percent no gross residual disease	Percent optimal residual disease	Median survival time (months)
[3][a] McGuire	1996	60	386	34.7	48	0	82.3	0.0	0.0	30.7
[32][a] Muggia	2000	59	614	30.0	67	0	73.6	0.0	0.0	27.6
[31][a] Markman	2001	59	462	0.0	100	51	78.4	35.5	100.0	57.6
[6][a] du Bois	2003	58	783	17.1	100	0	80.0	NR	62.0	43.0
[15][b] Eisenkop	2003	63	408	0.0	NR	0	NR	86.0	96.1	58.2
[5][a] Ozols	2003	56	792	0.0	100	0	86.0	35.5	100.0	49.0
[34][a] Rose	2004	58	424	5.7	100	0	95.0	0.0	0.0	36.0
[17][b] Aletti	2006	64	194	0.0	NR	0	100.0	23.7	67.5	42.1
[23][a] Armstrong	2006	56	415	0.0	100	49	62.7	36.9	100.0	66.9
[16][b] Chi	2006	60	465	0.0	NR	0	97.0	14.4	50.8	48.0
[30][a] du Bois	2006	59	1282	17.2	100	0	86.5	NR	60.0	43.5
[33][a] Pfisterer	2006	60	1308	16.9	100	0	86.5	NR	61.0	44.0
[28][b] Salani	2007	63	125	22.4	100	0	100.0	31.2	81.6	33.5
[35][a] Spriggs	2007	59	280	83.9	100	0	81.5	0.0	0.0	30.0
[24][a] Bookman	2009	59	4312	14.7	20	0	79.0	24.2	69.4	44.6
[27][b] Peiretti	2010	58	259	23.2	NR	0	92.0	44.0	76.1	57.6
[29][a] Vergote	2010	62	310	22.9	78.4	0	81.6	19.7	42.2	29.0
[25][b] Harter	2011	61	438	30.1	NR	0	NR	55.0	82.0	49.0

IP = intraperitoneal.
[a] Randomized controlled trial.
[b] Retrospective study.

Simple linear regression analysis of predictor variables

The results of simple linear regression analysis are shown in Table 2. The study period accrual time, median cohort age, proportion of patients receiving taxane chemotherapy, and proportion of patients completing 6-cycles of chemotherapy were not statistically significantly associated with median survival time. The surgical outcome predictor variables of no gross residual and optimal residual disease were both statistically significantly associated with median cohort survival time. Each 10% increase in the proportion of patients undergoing complete cytoreduction was associated with an increase in median cohort survival time of 3.8 months (95% confidence interval (CI) = 1.7–5.8 months, $p = 0.002$) (Fig. 1). Similarly, each 10% increase in the proportion of patients left with optimal residual disease was associated with a 2.5-month increase in median survival time (95%CI = 1.6–3.3 months, $p < 0.001$) (Fig. 2). Intraperitoneal chemotherapy was significantly associated with median survival time. Each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was associated with a 3.7-month increase in median cohort survival time (95%CI = 0.9–6.6 months, $p = 0.013$). There was a significant inverse relationship between stage IV disease and median survival time. Each 10% increase in the proportion of patients with stage IV disease was associated with a 3.7-month decrease in median survival time (95%CI = (−)6.2–(−)1.2 months, $p = 0.007$).

Multiple linear regression analysis of predictor variables

At the bivariate level, there was a strong positive correlation between the proportion of patients in each cohort undergoing optimal cytoreductive surgery and the proportion of patients undergoing complete cytoreductive surgery ($r = 0.82$, $p = 0.0002$). Model 1 multivariate linear regression analysis, using the surgical outcome criteria of no gross residual disease, revealed that each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was associated with a 3.9-month increase (95%CI = 1.1–6.8 months, $p = 0.008$) in median survival, and the proportion of patients undergoing complete cytoreduction was associated with a 2.3-month increase (95%CI = 0.6–4.0 months, $p = 0.01$) in median cohort survival time (Table 3). These were the only predictor variables significantly associated with, and independently predictive of survival. Substituting optimal residual disease as the surgical outcome criteria in the multivariate linear regression analysis (model 2) yielded similar directionality effects on the change in median cohort survival for all predictor variables; however, the relative magnitude of surgical outcome and intraperitoneal chemotherapy were attenuated compared to model 1. In model 2, each 10% increase in the proportion of patients left with optimal residual disease was associated with a statistically significant 1.8-month increase (95%CI = 0.6–3.0 months, $p = 0.004$) in median cohort survival time. Although each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was accompanied by a 2.7-month increase (95%CI = (−)0.1–5.4 months, $p = 0.057$) in median cohort survival, this effect was not statistically significant (Table 4).

Discussion

Meigs first described cytoreductive surgery for advanced ovarian cancer in 1934 [36]. Forty years later, Griffiths published a landmark study that conclusively demonstrated an inverse relationship between

Table 2
Simple linear regression analysis of change in predictor variable effects on median cohort survival time.

	Weighted mean	Range	Increment	Change in median survival (months)	95%CI	p-Value	Missing data (%)
Study year accrual midpoint	1999.2	1991 to 2004.5	(+) 1 year	0.5	(−) 0.8 to 1.7	0.443	0
Median age (years)	59.2	56 to 64	(+) 1 year	(−) 1.2	(−) 3.9 to 1.5	0.374	0
Percent taxane therapy	65.9	20% to 100%	(+) 10%	0.2	(−) 1.3 to 1.6	0.823	27.8
Percent IP therapy	3.3	0% to 51%	(+) 10%	3.7	0.9 to 6.6	0.013	0
Percent 6 cycles of therapy	82.5	62.7% to 100%	(+) 10%	(−) 2.0	(−) 8.4 to 4.4	0.512	11.1
Percent stage IV disease	15.7	0 to 83.9%	(+) 10%	(−) 3.7	(−) 6.2 to (−) 1.2	0.007	0
Percent no gross residual disease	25.9	0 to 86.0%	(+) 10%	3.8	1.7 to 5.8	0.002	16.7
Percent optimal residual disease	62.3	0 to 100%	(+) 10%	2.5	1.6 to 3.3	<0.0001	0
Median overall survival (months)	44.41	27.6 to 66.9	–	–	–	–	0

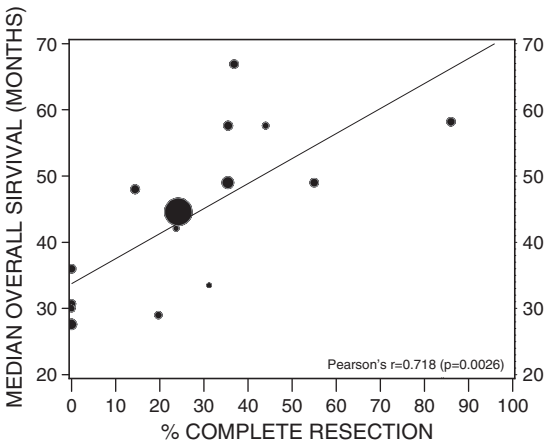


Fig. 1. Simple linear regression analysis: median cohort survival time plotted against the proportion of patients in each cohort undergoing complete cytoreductive surgery and left with no gross residual disease. Circle size is proportional to the number of subjects in each study, and the effects of other variables are ignored.

residual tumor diameter and patient survival [37]. Nearly every retrospective study and prospective study since then has demonstrated that the extent of residual disease and the use of platinum-based chemotherapy are key factors impacting survival in women with advanced staged ovarian cancer. In 1994, Hoskins et al., reporting for the GOG, definitively demonstrated the prognostic importance of a three-tiered classification system for residual disease: complete resection to no gross residual disease, optimal but visible (0.1 cm to ≤1 or 2 cm) residual disease, and suboptimal (>1 or 2 cm) residual disease, with the most favorable survival associated with complete resection [10]. The introduction of taxane chemotherapy into the frontline treatment regimen and the re-emergence of regional therapeutics (intraperitoneal chemotherapy) have further improved the expected survival outcome for women with advanced-stage ovarian cancer [22]. However, the relative survival impact of complete gross resection within the context of this more contemporary treatment paradigm has been difficult to define. Therefore, the objective of the current study was to examine the available literature using the technique of meta-analysis to quantify the effect on survival of surgical outcome criteria, and other prognostic variables, among patients with advanced-stage ovarian cancer treated during the platinum–taxane era.

The current analysis indicates that the two predictor variables associated with the largest effect on cohort survival were the proportion of patients in whom minimal residual disease was achieved and the proportion of patients receiving intraperitoneal chemotherapy. Although both no gross residual disease and optimal residual disease were significant and independent predictors of improved cohort survival, each 10% increase in the proportion of patients undergoing complete gross resection was associated with a 28% incremental improvement in the expected median survival time (2.3 months) compared to the proportion of patients left with optimal residual disease (1.8 months). These data offer an overarching population-based perspective on the magnitude of survival benefit associated with a progressively increasing percentage of patients with advanced-stage ovarian cancer achieving no gross residual disease prior to initiating chemotherapy.

The current data also validate and quantify the intuitive correlation between the specified surgical outcome criterion and the relative magnitude of the survival advantage associated with intraperitoneal chemotherapy. Applying the surgical outcome criterion of no gross residual disease, while controlling for the effects of other variables, was associated with a statistically significant and independent 3.9-month increase in median cohort survival for each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy. When optimal residual disease was used as the surgical outcome criterion, each 10% incremental change in the proportion of patients receiving regional treatment was reflected as a statistically non-significant 2.7-month increase in median cohort survival, after controlling for other variables. In other words, substituting optimal residual disease for no gross residual disease as the surgical outcome criterion resulted in a 44% reduction in the relative survival impact of each 10% incremental change in the proportion of patients receiving regional treatment. This observation underscores a GOG ancillary data analysis of protocols 114 and 172 recently reported by Landrum et al. [38]. In this dataset of patients with Stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy, complete resection of disease to microscopic residual was associated with a median overall survival time of 110 months, compared to

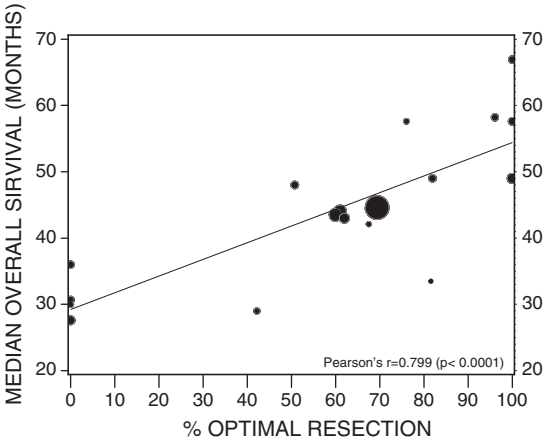


Fig. 2. Simple linear regression analysis: median cohort survival time plotted against the proportion of patients in each cohort undergoing optimal cytoreductive surgery. Circle size is proportional to the number of subjects in each study, and the effects of other variables are ignored.

Table 3
Model 1: multiple linear regression analysis of selected predictor variables versus median cohort survival time using no gross residual disease as the surgical outcome criteria.

	Increment	Change in median survival (months)	95%CI	p-Value
Study year accrual midpoint	(+) 1 year	0.5	(−) 0.4 to 1.3	0.246
Median age (years)	(+) 1 year	(−) 1.5	(−) 3.5 to 0.4	0.116
Percent taxane therapy	(+) 10%	(−) 0.4	(−) 1.5 to 0.8	0.494
Percent IP therapy	(+) 10%	3.9	1.1 to 6.8	0.008
Percent 6 cycles of therapy	(+) 10%	3.4	(−) 2.3 to 9.1	0.242
Percent stage IV disease	(+) 10%	(−) 1.0	(−) 3.2 to 1.1	0.339
Percent no gross residual disease	(+) 10%	2.3	0.6 to 4.0	0.011

Table 4
Model 2: multiple linear regression analysis of selected predictor variables versus median cohort survival time using optimal residual disease as the surgical outcome criteria.

	Increment	Change in median survival (months)	95%CI	p-Value
Study year accrual midpoint	(+) 1 year	0.2	(−) 0.7 to 1.1	0.645
Median age (years)	(+) 1 year	(−) 0.6	(−) 2.4 to 1.2	0.494
Percent taxane therapy	(+) 10%	0.1	(−) 1.0 to 0.9	0.903
Percent IP therapy	(+) 10%	2.7	0.1 to 5.4	0.057
Percent 6 cycles of therapy	(+) 10%	2.1	(−) 3.6 to 7.8	0.457
Percent stage IV disease	(+) 10%	(−) 0.4	(−) 2.8 to 2.0	0.721
Percent optimal residual disease	(+) 10%	1.8	0.6 to 3.0	0.004

55 months for patients with optimal but visible residual disease. Although the current analysis of collective data suggests that the positive survival effect of intraperitoneal chemotherapy is of greater magnitude when the more stringent residual disease criterion of complete gross resection is employed, the small number of patients receiving intraperitoneal chemotherapy may limit the robustness of this conclusion.

A critical review of the data presented must take into consideration the methodological limitations of a meta-analysis of this nature. First, every effort was made to include as many studies as possible while preserving the study selection criteria initially set forth. Nevertheless, the potential for selection bias, both with regard to studies selected for inclusion in the analysis as well as inclusion of patients within each individual study, must be considered. A second potential limitation is that the necessary imprecision of our predictor measurements may have affected our ability to discriminate between statistically and clinically meaningful differences. A third limitation is that the variety of chemotherapeutic agents and administration schedules precluded an analysis of total drug dose-intensity or cumulative drug dose. Similar meta-analyses of advanced ovarian cancer have not found these factors to have a significant effect on survival [39,40]. A fourth limitation of the current study is that we did not examine additional prognostic factors, such as surgical sub-stage for Stage III disease and performance status, that might have influenced either survival or the proportion of patients undergoing complete or optimal surgical cytoreduction. Expansion of the study selection criteria to include these factors would have markedly reduced the number of eligible studies. Finally, this study was limited to patient cohorts undergoing a standard therapeutic approach of initial surgery followed by adjuvant chemotherapy and was not intended to examine the clinical utility of primary surgery versus neoadjuvant chemotherapy.

Despite these limitations, there are several conclusions that can be drawn from the current analysis. First, for patients with advanced-stage ovarian cancer treated during the platinum–taxane era, the proportion of patients left with no gross residual disease is associated with an incremental survival advantage of greater magnitude compared to the proportion of patients left with optimal residual disease. Second, the proportion of patients receiving intraperitoneal chemotherapy is a significant and independent predictor of cohort survival time. And finally, the relatively greater survival benefit associated with intraperitoneal chemotherapy in the context of no gross residual disease highlights the dependency of regional therapeutic efficacy on the completeness of surgical resection.

Conflict of interest statement

The authors do not have any potential conflicts of interest.

Acknowledgment

Dr. Robert E. Bristow was supported by the Queen of Hearts Foundation.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Shih KK, Chi DS. Maximal cytoreductive effort in epithelial ovarian cancer surgery. J Gynecol Oncol 2010;21:75–80.
[3] McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6.
[4] Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin–paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699–708.
[5] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al. 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.
[6] du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320–9.
[7] Fader AN, Rose PG. Role of surgery in ovarian carcinoma. J Clin Oncol 2007;25:2873–83.
[8] 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.
[9] Omura GA, Bundy BN, Berek JS, Curry S, Delgado G, Mortel R. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 1989;7:457–65.
[10] Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma.Am J Obstet Gynecol 1994;170:974–9 [discussion 9–80].
[11] Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? Gynecol Oncol 2001;82:489–97.
[12] Stoeckle E, Paravis P, Floquet A, Thomas L, Tunon de Lara C, Bussieres E, et al. Number of residual nodules, better than size, defines optimal surgery in advanced epithelial ovarian cancer. Int J Gynecol Cancer 2004;14:779–87.
[13] 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.
[14] Skirnisdottir I, Sorbe B. Prognostic factors for surgical outcome and survival in 447 women treated for advanced (FIGO-stages III–IV) epithelial ovarian carcinoma. Int J Oncol 2007;30:727–34.
[15] 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.
[16] 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 (EOC)? Gynecol Oncol 2006;103:559–64.
[17] 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.
[18] Winter III WE, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:3621–7.
[19] Winter III WE, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2008;26:83–9.
[20] du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115:1234–44.
[21] Wimberger P, Wehling M, Lehmann N, Kimmig R, Schmalfeldt B, Burges A, et al. Influence of residual tumor on outcome in ovarian cancer patients with FIGO stage IV disease: an exploratory analysis of the AGO-OVAR (Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group). Ann Surg Oncol 2010;17:1642–8.
[22] Chang SJ, Bristow RE. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease. Gynecol Oncol 2012;125:483–92.
[23] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
[24] Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol 2009;27:1419–25.
[25] Harter P, Muallem ZM, Buhrmann C, Lorenz D, Kaub C, Hils R, et al. Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer. Gynecol Oncol 2011;121:615–9.
[26] Kommoss S, Rochon J, Harter P, Heitz F, Grabowski JP, Ewald-Riegler N, et al. Prognostic impact of additional extended surgical procedures in advanced-stage primary ovarian cancer. Ann Surg Oncol 2010;17:279–86.
[27] Peiretti M, Zanagnolo V, Aletti GD, Bocciolone L, Colombo N, Landoni F, et al. Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: surgical and oncological outcomes. Single institution experience. Gynecol Oncol 2010;119:259–64.
[28] Salani R, Zahurak ML, Santillan A, Giuntoli II RL, Bristow RE. Survival impact of multiple bowel resections in patients undergoing primary cytoreductive surgery for advanced ovarian cancer: a case–control study. Gynecol Oncol 2007;107:495–9.
[29] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Eng J Med 2010;363:943–53.
[30] du Bois A, Weber B, Rochon J, Meier W, Goupil A, Olbricht S, et al. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol 2006;24:1127–35.

[31] Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001–7.
[32] 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.
[33] Pfisterer J, Weber B, Reuss A, Kimmig R, du Bois A, Wagner U, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. J Natl Cancer Inst 2006;98:1036–45.
[34] Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med 2004;351:2489–97.
[35] Spriggs DR, Brady MF, Vaccarello L, Clarke-Pearson DL, Burger RA, Mannel R, et al. Phase III randomized trial of intravenous cisplatin plus a 24- or 96-hour infusion of paclitaxel in epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:4466–71.
[36] Meigs JV. Tumors of the female pelvic organs. New York: MacMillan; 1934 .
[37] Griffith CT. Surgical resection of tumor bulk in the treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975;42:101–4.
[38] Landrum L, Java J, Matthews C, Lanneau G, Copeland L, Armstrong D, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. Abstract 56. Gynecol Oncol 2012;125:S24.
[39] Hunter RW, Alexander NDE, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis? Am J Obstet Gynecol 1992;166:504–11.
[40] Ben-David Y, Rosen B, Franssen E, Einarson T, Szyfer I. Meta-analysis comparing cisplatin total dose intensity and survival. Gynecol Oncol 1995;59:93–101.