Published in final edited form as:

Gynecol Oncol. 2018 October ; 151(1): 18–23. doi:10.1016/j.ygyno.2018.07.021.

Does Adjuvant Chemotherapy Dose Modification Have an Impact On the Outcome of Patients diagnosed with Advanced Stage Ovarian Cancer? An NRG Oncology/Gynecologic Oncology Group Study

Alexander B. Olawaiye, MD¹, James J. Java, PhD², Thomas C. Krivak, MD³, Michael Friedlander, MD⁴, David G. Mutch, MD⁵, Gretchen Glaser, MD⁶, Melissa Geller, MD⁷, David M. O'Malley, MD⁸, Robert M. Wenham, MD⁹, Roger B. Lee, MD¹⁰, Diane C. Bodurka, MD¹¹, Thomas J. Herzog, MD¹², and Michael A. Bookman, MD¹³

¹Division of Gynecologic Oncology; Magee-Womens Hospital of UPMC, Pittsburgh, PA olawaiyea@mail.magee.edu ²NRG Oncology; Clinical Trial Development Division; Biostatistics & Bioinformatics; Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263 james.j.java@gmail.com ³Division of Gynecologic Oncology, Department of Obstetrics and Gynecology; The Western Pennsylvania Hospital, Pittsburgh, PA thomas.krivak@ahn.org ⁴Prince of Wales Clinical School UNSW; Department of Medical Oncology; The Prince of Wales Hospital; Sydney, AU michael.friedlander@sesiahs.health.nsw.gov.au ⁵Dept. of Obstetrics and Gynecology; Washington University School of Medicine; Saint Louis, MO 63110 mutchd@wudosis.wustl.edu ⁶Gynecologic Oncology; Carilion Clinic Gynecological Oncology; Roanoke, VA 24016 geglaser@carilionclinic.org ⁷Dept. of Obstetrics, Gynecology and Women's Health; University of Minnesota Medical Center-Fairview; Minneapolis, MN 55455 gelle005@umn.edu ⁸Dept. of Obstetrics and Gynecology; The Ohio State University Comprehensive Cancer Center; Columbus, OH 43210 omalley.46@osu.edu ⁹Department of Gynecologic Oncology; Moffitt Cancer Center and Research Institute; Tampa, FL 33612 robert.wenham@moffitt.org ¹⁰Tacoma General Hospital; Tacoma, WA rogerblee@aol.com ¹¹Department of Gynecologic Oncology and

Corresponding author: Alexander B. Olawaiye, MD, University of Pittsburgh/Magee-Womens Hospital of UPMC, Division of Gynecologic Oncology, 300 Halket Street, Pittsburgh, PA 15213, Phone: 412 641-5468, Fax: 412 641-5417, olawaiyea@mail.magee.edu.

AUTHOR CONTRIBUTIONS

All authors provided data, were involved in writing, revision, and approved the final manuscript. James Java performed the statistical analyses of this study.

CONFLICT OF INTEREST STATEMENT

Dr. Michael Friedlander is on the advisory board for Astra Zeneca.

Dr. David O'Malley is on the advisory board at Myriad, Clovis, Astra Zeneca, Novocure, Tesaro and Janssen. He also serves on the steering committee at Amgen.

Dr. Thomas Herzog serves on the advisory board and is also a consultant for Astra Zeneca, Clovis, Genentech and Tesaro.

Dr. Michael Bookman reports personal fees from McKesson Specialty Health and USOR, from Genentech-Roche, personal fees from Mateon, personal fees from AstraZeneca, personal fees from AbbVie, personal fees from Tesaro, personal fees from Clovis, personal fees from Pfizer, outside the submitted work.

All other co-authors have no conflicts of interest to declare.

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Reproductive Medicine; The University of Texas MD Anderson Cancer Center; Houston, TX 77030 dcbodurka@mdanderson.org ¹²Dept. of Obstetrics & Gynecology; University of Cincinnati Cancer Institute; University of Cincinnati, Cincinnati, OH 45267 herzogtj@ucmail.uc.edu ¹³US Oncology Research, Arizona Oncology, Tucson, AZ 85711 michael.bookman@usoncology.com

Abstract

PURPOSE: To determine the relationship between chemotherapy dose modification (dose adjustment or treatment delay), overall survival (OS) and progression-free survival (PFS) for women with advancedstage epithelial ovarian carcinoma (EOC) and primary peritoneal carcinoma (PPC) who receive carboplatin and paclitaxel.

METHODS: Women with stages III and IV EOC and PPC treated on the Gynecologic Oncology Group phase III trial, protocol 182, who completed eight cycles of carboplatin with paclitaxel were evaluated in this study. The patients were grouped per dose modification and use of granulocyte colony stimulating factor (G-CSF). The primary end point was OS; Hazard ratios (HR) for PFS and OS were calculated for patients who completed eight cycles of chemotherapy. Patients without dose modification were the referent group. All statistical analyses were performed using the R programming language and environment.

RESULTS: A total of 738 patients were included in this study; 229 (31%) required dose modification, 509 did not. The well-balanced for demographic and prognostic factors. The adjusted hazard ratios (HR) for disease progression and death among dose-modified patients were: 1.43 (95% CI, 1.19–1.72, $P < 0.001$) and 1.26 (95% CI, 1.04–1.54, $P = 0.021$), respectively. Use of G-CSF was more frequent in dose-modified patients with an odds ratio (OR) of 3.63 (95% CI: 2.51–5.26, $P < 0.001$) compared to dose-unmodified patients.

CONCLUSION: Dose-modified patients were at a higher risk of disease progression and death. The need for chemotherapy dose modification may identify patients at greater risk for adverse outcomes in advanced stage EOC and PPC.

Keywords

Ovarian cancer; chemotherapy; dose reduction; dose modification; progression; G-CSF

INTRODUCTION

Worldwide, 205,000 new ovarian cancer cases are diagnosed leading to 125,000 deaths annually making it the most lethal gynecologic malignancy.¹ In the United States there were 22,280 new cases and 14,240 deaths in 2016.² The standard approach utilized in treating patients with advanced stage epithelial ovarian carcinoma (EOC) is primary cytoreductive surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy with interval cytoreductive surgery.³ Chemotherapy with carboplatin and paclitaxel remains the standard of care for patients with a new diagnosis of advanced stage EOC, in spite of extensive investigation of alternative treatment approaches and combinations.

Despite the excellent response rates and major advances made in the treatment of EOC and primary peritoneal carcinoma (PPC), the five-year overall survival (OS) is a modest 46%.⁴ The reasons for this poor outcome is due to patients presenting with advanced stage disease and the fact that the majority of patients with advanced stage EOC and PPC will experience disease relapse after achieving an initial remission. Also, following recurrence, the vast majority of patients eventually develop chemoresistance. An adjustment of chemotherapy dose and schedule has been investigated in previous clinical trials. Increasing the number of cycles or the dose of chemotherapy per cycle has not resulted in any significant therapeutic advantage in terms of progression-free survival (PFS) or OS.⁵ It has been previously shown that similar outcomes were seen in patients treated with 5 versus 12 cycles of chemotherapy.^{6–9} Nonetheless, there are reasons to believe that completing the number of prescribed chemotherapy cycles on schedule without dose reduction may be associated with improved clinical outcomes. It is believed that only a proportion of malignant cells in a tumor are dividing and therefore vulnerable to chemotherapy at any given time. If these cells are not treated on schedule or are treated with a lower dose of chemotherapy, only sub-lethal damages are inflicted on the cancer cells. Theoretically, further chemotherapy dose delay and/or reduction allow such sub-lethal damages to be repaired. This concept has been evaluated in patients with breast cancer and studies have shown that completion of chemotherapy on schedule and above relative dose intensity thresholds improve patients' outcomes.^{10–12} Also, Rabbie Hanna et al. in a multicenter retrospective study investigated the impact of relative dose intensity in ovarian cancer patients, the commonest regimen in their study was carboplatin and paclitaxel, despite adjustments for established prognostic factors, reduced relative dose intensity was associated with reduced overall survival¹³

During the period of this analysis, the most common chemotherapy regimen used for advanced stage EOC and PPC was intravenous carboplatin, typically at an area under the curve (AUC) of 6, and paclitaxel at 175 mg /m² body surface area. This combination therapy was administered every three weeks for a total of six to eight cycles. The primary objective of this study was to evaluate the impact, if any, of dose modification on the outcome of ovarian cancer treatment in terms of PFS and OS. Patients treated on the control arm of the GOG-182 served as the subjects of this study.¹⁴ Dose modification in this study is described as chemotherapy dose reduction (15% of cycle 1 dose) or cycle delay (3 weeks) or both. We also compared PFS and OS in patients who required granulocyte colony stimulating factor (G-CSF) with those of patients who did not.

PATIENTS AND METHODS

Patient Selection

Eligible patients for this study were women diagnosed with International Federation of Gynecologists and Obstetricians (FIGO) stages III and IV EOC or PPC who enrolled into GOG-182, a randomized controlled phase III trial. These women underwent optimal or sub-optimal cytoreductive surgery and were subsequently randomized to one of five treatment arms of intravenous platinum doublet or triplet chemotherapy regimens.¹⁴ We embarked on this study following approval of the GOG Ancillary Data Committee.

The reference arm for GOG-182 was carboplatin (AUC of 6) and paclitaxel (175 mg/m²). The intended number of cycles in all arms was eight. Patients who experienced significant toxicity were to be initially managed with chemotherapy dose modification (DM) consisting of dose reduction and/or cycle delay. Growth factors (mainly G-CSF) were utilized if toxicity persisted despite dose modification (DM). Some patients received G-CSF prophylactically and therefore a sub-group of patients who had no DM were treated with G-CSF.

The subjects of this study were patients who completed eight cycles of chemotherapy with or without DM. This group was chosen to allow for statistically valid comparison of treatment outcome in patients who required DM versus those who did not. For the purposes of this study, dose reduction was defined as a change of dose to 0.85 or less of that given in the first cycle whereas chemotherapy dose delay was defined as a protraction of the eight cycles of chemotherapy beyond 24 weeks; the expected duration of eight chemotherapy cycles without delay was 21 weeks. Chemotherapy DM is defined as dose reduction or cycle delay or a combination of both.

The selected study population was then divided into two main groups; group 1 (dose-unmodified) consisted of patients who completed all the assigned eight cycles of chemotherapy with full dose administered on-schedule, and group 2 (dose-modified) consisted of patients who completed all eight cycles but required DM. Further sub-grouping was done to evaluate the potential impact of G-CSF as follows; group 3 had no DM and no G-CSF, group 4 had no DM but received G-CSF, Group 5 had DM but no G-CSF and group 6 had both DM and G-CSF.

Regarding platelets nadir and absolute neutrophil count nadir, we have only limited and noisy data, these limited data doesn't integrate well into the time-varying survival models we created.

Statistical Design

Categorical variables were compared between groups by the Pearson chi-square test, and continuous variables by the Wilcoxon–Mann–Whitney test. Survival was estimated using the Kaplan–Meier and extended Kaplan–Meier methods.

The Cox proportional hazards model was used to evaluate independent prognostic factors and to estimate their covariate-adjusted effects on PFS and OS. To account for the changing risk associated with dose modification over time, a binary (yes/no) indicator of dose modification was entered into the Cox model as a time-varying covariate (as were binary indicators of the administration of G-CSF and of interval cytoreduction after cycle four, and also the number of cycles of chemotherapy completed). Time-varying covariate analysis relates the risk of death to the most recent covariate measures rather than to the baseline measures only, and mitigates the problem of analysis by response, in which covariate and endpoint are confounded through both being outcomes of treatment. Because approximately 5% of the patients had at least one prognostic factor missing, missing values were generated by simple imputation before modeling, under the assumption of data missing at random (MAR). The nonlinearity of the effect of continuous variables was assessed using restricted

cubic splines. All statistical tests were two-tailed with the significance level set at $\alpha=0.05$, except where noted. Statistical analyses were performed using the R programming language and environment.

RESULTS

There were 738 evaluable patients, all of whom had complete data on DM status. DM was required in 229 (31%) patients; the remaining 509 (69%) patients completed their eight cycles of chemotherapy without DM. Overall, the characteristics of patients were mostly similar across the two main groups (Table 1). Performance status of dose-unmodified patients was better with 279 patients (54%) documented as normal /asymptomatic compared to 99 (43%) of the DM patients (Table 2). Also, G-CSF use was more prevalent among dose-modified patients, 92 (40.2%) vs. 123 (24.2%) patients, $P < 0.001$.

Tables 2 and 3 respectively compare the PFS and OS of DM patients (from the patient population and with DM as described above) against the survival of dose-unmodified patients from the same population. When dose-unmodified patients were used as the referent, the adjusted hazard ratio (HR) for disease progression in dose-modified patients was 1.43 (95% CI, 1.19–1.72, $P < 0.001$). Likewise, the adjusted HR for death in DM patients was 1.26 (95% CI, 1.04–1.54, $P = 0.021$).

In survival models that included an interaction between the indicators for dose modification and the administration of G-CSF, the interaction term was not statistically significant, suggesting that neither dose-modification subgroup had a preferential benefit from the use of G-CSF. In addition, our analyses did not show any impact of G-CSF use in sub-groups 3–6 (data not shown).

The covariate-adjusted Kaplan-Meier (KM) curves for PFS and OS according to DM status are shown in Figure 1 and Figure 2. The median PFS of dose-unmodified patients was 17.55 months (95% CI, 16.46–19.1 months), and that of DM patients was 9.92 months (95% CI, 6.67–12.5 months), $P < 0.001$. The median OS of dose-unmodified patients was 48.0 months (95% CI, 42.7–53.3 months), and that of DM patients was 28.7 months (95% CI, 22.3–35.0 months), $P = 0.021$.

Logistic regression showed that patients in the DM group had odds of receiving G-CSF 263% greater than those in the dose-unmodified group (OR=3.63, 95% CI: 2.51–5.26, $P < 0.001$). For survival models considering a maximum of 6 cycles of therapy, when dose-unmodified patients were used as the referent, the adjusted hazard ratio (HR) for disease progression in dose-modified patients was 1.50 (95% CI, 1.27–1.78, $P < 0.001$). Likewise, the adjusted HR for death in DM patients was 1.40 (95% CI, 1.17–1.68, $P < 0.001$). Tables 4 and 5.

DISCUSSION

This ancillary data analysis of GOG-182 indicates that both PFS and OS were significantly associated with dose modification. Both of these outcome measures were significantly reduced in DM patients (PFS by 7.6 months and OS by 19.3 months). Our findings are

consistent with the findings of similar studies conducted in other cancer sites.^{15,16} The definition of DM patients in this study was a 15% reduction in intended dosage or those who required an additional three weeks or longer to complete the total prescribed number of chemotherapy cycles. It is likely that if lower/more prolonged cut-offs were utilized, the adverse effect of DM would have been greater.

There have been significant improvements in the treatment of patients with advanced EOC and PPC with increases in median survival over the last three decades, but without an impact on disease-related mortality in the setting of metastatic disease. Five-year OS for patients with advanced stage EOC increased from 37% in 1977 to 45% in 2006.¹⁷ This improvement can be ascribed to increased utilization of maximal cytoreductive surgery¹⁸ combined with platinum-based chemotherapy^{19–22}, addition of taxanes^{23–28}, combination of intravenous and intraperitoneal chemotherapy, and access to novel agents in the setting of recurrent disease,²⁹ as well as general improvements in supportive care. However, the five-year survival among elderly patients with EOC is known to be poorer, although age-related comparisons are limited by the small number of elderly patients enrolled on clinical trials. Certainly, comorbidities may contribute to suboptimal administration of chemotherapy in many elderly patients.^{30,31} Our current data demonstrated the importance of avoiding DM if at all possible.

Data from other cancer sites suggest that relative dose intensity significantly impacts both PFS and OS of patients who require chemotherapy, although much of the data are retrospective, and prospective trials of dose intensity have not been associated with improved long-term clinical outcomes in ovarian cancer.^{10–12,15,16} Such data make it imperative to prospectively evaluate the impact of DM in patients with advanced stage EOC. Hematologic toxicity is one of the most important reasons for chemotherapy DM. Theoretically, G-CSF and other bone marrow stimulants may be used prophylactically to reduce bone marrow toxicity thereby eliminating or at least reducing the need for DM in EOC patients, especially if DM may adversely affect PFS or OS. However, G-CSF can also increase the cumulative risk of carboplatin-induced thrombocytopenia (which is not protected), add toxicities including bone pain, and substantially increase the overall financial burden of treatment.

One important and unanswered clinical question in this study is whether the prophylactic use of growth factors to maintain relative dose intensity among patients experiencing hematologic toxicity would have resulted in the same outcome compared to patients who did not receive growth factors. However, the design of the original trial does not make it possible to adequately answer this important question since patients experiencing hematologic toxicity were supposed to have DM as an initial step prior to utilization of growth factors. The protocol stated: “In general, patients will not receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with clinical treatment guidelines.” Nonetheless, 123 (24%) of the dose-unmodified group were treated with G-CSF

and able to complete their prescribed dose and cycles of chemotherapy on schedule. This suggests that sustaining relative dose intensity could be beneficial to outcome regardless of how it is achieved. Clearly this hypothesis would require testing in a prospective fashion. Of note, G-CSF regulatory approval was based on a reduction in the risk of febrile neutropenic complications, rather than improved clinical outcomes, and it has not been prospectively demonstrated that prophylactic G-CSF improves OS in patients with metastatic solid tumors.

Most recent phase III trials in patients with advanced stage EOC utilize six cycles of chemotherapy. GOG-182, from which our data was derived, was designed with eight cycles of chemotherapy in order to better assess efficacy and toxicity of the sequential doublet and triplet combinations. As a means to assure the generalizability of these findings to patients who are scheduled to receive only six cycles, the data were analyzed also in patients after six cycles of chemotherapy. The findings were strikingly similar (Tables 4 and 5).

The findings of this retrospective study are hypothesis-generating, but raise clinically relevant questions. In particular, should women undergoing treatment for EOC be informed that their survival may be impacted by DM? This cannot be definitively answered within the context of a retrospective analysis in view of the potential impact of confounding variables, including nutritional status, hypoalbuminemia, physiologic age, performance status, and ascites. However, it seems reasonable to recommend that efforts should be made to complete planned chemotherapy in a timely fashion with fullyprescribed dosing. Second, this study suggests that use of G-CSF in patients experiencing hematologic toxicity prior to DM may represent a better approach than DM as an initial step. It would have been interesting to evaluate patients who did not actually complete all the assigned chemotherapy cycles using the patients who completed treatment as the referent group. This was not possible, however, because of the outcome-by-outcome confounding of dose modification and survival, which was necessarily mitigated through landmark analysis; and also the influence of other factors not readily controlled for in a retrospective analysis. Nonetheless, this question of how to best maintain chemotherapy dosing and maximize dose density is an important question that requires prospective study.

Although this study is based on data from a prospective trial, an important limitation of the study is its retrospective nature with all the well-known disadvantages of retrospective data analysis. The methods section for GOG-182 instructed that in patients experiencing significant toxicity, chemotherapy dose reduction was to be used first before adding G-CSF to their treatment if toxicity persisted; however, a large group of patients in this study were given G-CSF without any dose reduction. This indicates that many treating physicians did not adhere to the protocol guidelines. It is possible that this failure to adhere to the protocol may have diluted the impact of DM. Therefore the magnitude of the impact of DM seen in this study could have been greater.

In conclusion, this study underscores the importance of enabling patients undergoing treatment for advanced Stage EOC and PPC with chemotherapy to avoid dose modifications where feasible. The results from our current study are hypothesis generating and require validation. The decrease in PFS and OS that was seen in the patient undergoing DM is concerning and the role of hematologic growth factors in maintaining relative dose intensity

remains unclear from this analysis. This question is unlikely to be addressed in future randomized trials, in view of current clinical priorities and resources.

Acknowledgments

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical Office (CA 37517), NRG Oncology SDMC (U10 CA180822) and NRG Operations (U10CA180868). The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California at Los Angeles, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group P.C., University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St. Luke's Medical Center, University of Kentucky, Eastern Virginia Medical School, The Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, P.C., Southwestern Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Columbus Cancer Council, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Eastern Collaborative Oncology Group, Thomas Jefferson University Hospital, Case Western Reserve University, and Tampa Bay Cancer Consortium.

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HIGHLIGHTS

- Chemotherapy dose modification is common in ovarian cancer treatment
- Patients requiring dose modification are more likely to require growth factor
- Dose modified patients are at a higher risk of worse treatment outcome

Figure 1:
Extended Kaplan–Meier curves of progression-free survival in the control arm of GOG-0182, stratified by a time-varying indicator of dose modification. Figures below months indicate the numbers of patients at risk.

Figure 2: Extended Kaplan-Meier curves of overall survival in the control arm of GOG-0182, stratified by a time-varying indicator of dose modification. Figures below months indicate the numbers of patients at risk.

Table 1:**Patients' Characteristics by Dose Modification**

	N	no N = 509	yes N = 229	Test Statistic
Age years	738	50.4 57.8 65.3	51.4 58.0 68.3	$P = 0.127^1$
Race/Ethnicity	738			$P = 0.074^2$
White		89.8% (457)	89.1% (204)	
Black		4.1% (21)	6.1% (14)	
Hispanic		3.9% (20)	1.3% (3)	
Asian		1.2% (6)	3.1% (7)	
other		1.0% (5)	0.4% (1)	
BMI kg/m ²	705	22.5 25.9 29.8	22.3 25.1 29.3	$P = 0.211^1$
Performance status	738			$P = 0.001^2$
normal, asymptomatic		54.8% (279)	43.2% (99)	
symptomatic, ambulatory		40.1% (204)	45.9% (105)	
symptomatic, in bed < 50%		5.1% (26)	10.9% (25)	
Top-level FIGO stage	738			$P = 0.059^2$
III		85.1% (433)	79.5% (182)	
IV		14.9% (76)	20.5% (47)	
Tumor grade (differentiation)	724			$P = 0.968^2$
good		7.2% (36)	7.7% (17)	
moderate		35.4% (178)	35.3% (78)	
poor		57.5% (289)	57.0% (126)	
Histology	738			$P = 0.546^2$
serous adenocarcinoma		82.7% (421)	84.3% (193)	
mixed epithelial carcinoma		5.1% (26)	4.4% (10)	
endometrioid adenocarcinoma		5.9% (30)	3.1% (7)	
clear-cell carcinoma		2.2% (11)	3.5% (8)	
mucinous adenocarcinoma		1.6% (8)	1.7% (4)	
other		2.6% (13)	3.1% (7)	
Tumor residual	738			$P = 0.365^2$
microscopic		23.2% (118)	20.1% (46)	
optimal (0.1–1 cm)		50.1% (255)	48.5% (111)	
suboptimal (> 1 cm)		26.7% (136)	31.4% (72)	
CA-125 ug/mL	721	88.6 214.0 520.0	100.8 214.5 778.8	$P = 0.427^1$
Ascites	716			$P = 0.909^2$
no		23.5% (116)	23.9% (53)	
yes		76.5% (378)	76.1% (169)	
Given G-CSF?	738			$P < 0.001^2$
no		75.8% (386)	59.8% (137)	
yes		24.2% (123)	40.2% (92)	
Interval cytoreduction	738			$P = 0.101^2$

	N	no N = 509	yes N = 229	Test Statistic
no		96.9% (493)	94.3% (216)	
yes		3.1% (16)	5.7% (13)	

Table 2:**Multivariate Progression-Free Survival Analysis (CP Arm)**

Covariate	AHR	95% CI	<i>p</i> *
Dose modification			< 0.001
no	1.00	<i>referent</i>	
yes	1.43	1.19–1.72	
Age (years) [†]	1.01	1.00–1.02	0.020
Race/Ethnicity			0.395
White	1.00	<i>referent</i>	
other	0.89	0.69–1.16	
Performance status			0.082
0	1.00	<i>referent</i>	
1	1.03	0.87–1.22	
2	1.43	1.04–1.96	
Histology			0.001
serous	1.00	<i>referent</i>	
mixed epithelial	0.94	0.65–1.35	
endometrioid	1.31	0.91–1.89	
clear-cell/mucinous	2.29	1.53–3.44	
other	1.29	0.80–2.08	
Stage			0.046
III	1.00	<i>referent</i>	
IV	1.25	1.00–1.55	
CA-125 ($\mu\text{g/mL}$) [‡]	1.01	1.01–1.02	< 0.001
Ascites			0.322
no	1.00	<i>referent</i>	
yes	1.10	0.91–1.35	
Tumor residual			< 0.001
microscopic	1.00	<i>referent</i>	
1 cm	1.55	1.25–1.93	
> 1 cm	1.89	1.46–2.44	
Interval cytoreduction			0.259
no	1.00	<i>referent</i>	
yes	0.79	0.53–1.19	
Given G-CSF			0.909
no	1.00	<i>referent</i>	
yes	0.99	0.81–1.21	
Chemo. cycles [§]	0.91	0.85–0.99	0.020

* The *p*-values are from the overall test of significance of each covariate in the model.

[†] The AHR denotes the change in risk of progression or death associated with an increase of 1 year in age.

[‡]The AHR denotes the change in risk of progression or death associated with a 10% increase in CA-125 (gg/mL).

[§]The AHR denotes the change in risk of progression or death associated with an increase of 1 cycle of chemotherapy.

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Table 3:**Multivariate Overall Survival Analysis (CP Arm)**

Covariate	AHR	95% CI	<i>p</i> *
Dose modification			0.021
no	1.00	<i>referent</i>	
yes	1.26	1.04–1.54	
Age (years) [†]	1.01	1.01–1.02	0.001
Race/Ethnicity			0.927
White	1.00	<i>referent</i>	
other	0.99	0.75–1.30	
Performance status			0.024
0	1.00	<i>referent</i>	
1	1.05	0.88–1.26	
2	1.58	1.13–2.19	
Histology			< 0.001
serous	1.00	<i>referent</i>	
mixed epithelial	1.02	0.69–1.51	
endometrioid	0.99	0.65–1.50	
clear-cell/mucinous	2.72	1.82–4.06	
other	1.46	0.90–2.38	
Stage			0.012
III	1.00	<i>referent</i>	
IV	1.34	1.07–1.68	
CA-125 (wg/mL) [‡]	1.01	1.00–1.02	0.001
Ascites			0.100
no	1.00	<i>referent</i>	
yes	1.20	0.97–1.48	
Tumor residual			< 0.001
microscopic	1.00	<i>referent</i>	
< 1 cm	1.62	1.27–2.07	
> 1 cm	1.73	1.30–2.29	
Interval cytoreduction			0.035
no	1.00	<i>referent</i>	
yes	0.61	0.39–0.97	
Given G-CSF			0.399
no	1.00	<i>referent</i>	
yes	1.10	0.88–1.36	
Chemo. cycles [§]	0.85	0.79–0.91	< 0.001

* The *p*-values are from the overall test of significance of each covariate in the model.

[†] The AHR denotes the change in risk of death associated with an increase of 1 year in age.

[†]The AHR denotes the change in risk of death associated with a 10% increase in CA-125 (gg/mL).

[§]The AHR denotes the change in risk of death associated with an increase of 1 cycle of chemotherapy.

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Table 4:

Multivariate Progression-Free Survival Analysis (CP Arm) [Analysis limited to the first 6 cycles of chemotherapy]

	β	HR	2.5 %	97.5 %	<i>p</i>
had dose modification: yes	0.408	1.504	1.269	1.784	< 0.001
age	0.009	1.009	1.002	1.016	0.017
race: other	-0.123	0.884	0.681	1.148	0.356
performance: symptomatic, ambulatory	0.029	1.030	0.871	1.217	0.730
performance: symptomatic, in bed < 50%	0.357	1.428	1.042	1.959	0.027
histology: mixed epithelial	-0.085	0.918	0.637	1.323	0.648
histology: endometrioid	0.266	1.304	0.905	1.881	0.154
histology: clear-cell/mucinous	0.803	2.231	1.492	3.338	< 0.001
histology: other	0.224	1.251	0.772	2.027	0.364
stage IV	0.222	1.248	1.006	1.549	0.044
CA-125	0.130	1.139	1.076	1.205	< 0.001
ascites: yes	0.105	1.111	0.911	1.354	0.298
residual: optimal (0.1–1 cm)	0.436	1.547	1.243	1.925	< 0.001
residual: suboptimal (> 1 cm)	0.633	1.883	1.455	2.438	< 0.001
had interval cytoreduction: yes	-0.219	0.803	0.539	1.198	0.283
got G-CSF: yes	-0.064	0.938	0.767	1.147	0.535
cycles	-0.165	0.848	0.755	0.952	0.005

Table 5:

Multivariate Overall Survival Analysis (CP Arm) [Limited to the first 6 cycles of chemotherapy]

	β	HR	2.5 %	97.5 %	p
had dose modification: yes	0.339	1.403	1.169	1.684	< 0.001
age	0.013	1.013	1.005	1.021	0.001
race: other	-0.000	1.000	0.756	1.321	0.997
performance: symptomatic, ambulatory	0.047	1.048	0.874	1.257	0.610
performance: symptomatic, in bed < 50%	0.445	1.561	1.124	2.167	0.008
histology: mixed epithelial	0.027	1.027	0.694	1.520	0.893
histology: endometrioid	-0.022	0.978	0.643	1.488	0.918
histology: clear-cell/mucinous	0.988	2.685	1.803	3.999	< 0.001
histology: other	0.379	1.461	0.898	2.377	0.127
stage IV	0.301	1.351	1.078	1.693	0.009
CA-125	0.105	1.111	1.043	1.183	0.001
ascites: yes	0.185	1.203	0.971	1.490	0.091
residual: optimal (0.1–1 cm)	0.478	1.613	1.264	2.059	< 0.001
residual: suboptimal (> 1 cm)	0.545	1.724	1.299	2.289	< 0.001
had interval cytoreduction: yes	-0.471	0.624	0.395	0.988	0.044
got G-CSF: yes	0.081	1.085	0.876	1.343	0.456
cycles	-0.224	0.799	0.725	0.882	< 0.001