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Neoadjuvant chemotherapy and primary debulking surgery utilization for advanced-stage ovarian cancer at a comprehensive cancer center

Jennifer J. Mueller^a, Qin C. Zhou^b, Alexia Iasonos^b, Roisin E. O'Cearbhaill^{c,d}, Farah A. Alvi^a, Amr El Haraki^a, Ane Gerda Zahl Eriksson^a, Ginger J. Gardner^{a,e}, Yukio Sonoda^{a,e}, Douglas A. Levine^{a,e}, Carol Aghajanian^{c,d}, Dennis S. Chi^{a,e}, Nadeem R. Abu-Rustum^{a,e}, and Oliver Zivanovic^{a,e,*}

^a Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^b Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^c Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States

^d Department of Medicine, Weill Cornell Medical College, New York, NY, United States

^e Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, United States

Abstract

Objective—The aim of this study was to evaluate the use of neoadjuvant chemotherapy (NACT) and primary debulking surgery (PDS) before and after results from a randomized trial were published and showed non-inferiority between NACT and PDS in the management of advanced-stage ovarian carcinoma.

Methods—We evaluated consecutive patients with advanced-stage ovarian cancer treated at our institution from 1/1/08–5/1/13, which encompassed 32 months before and 32 months after the randomized trial results were published. We included all newly diagnosed patients with high-grade histology and stage III/IV disease. Associations between the use of NACT and clinical variables over time were evaluated.

Results—Our study included 586 patients. Median age was 62 years (range, 30–90); 406 patients (69%) had stage III disease, and 570 (97%) had disease of serous histology. Twenty-six percent (154/586) were treated with NACT and 74% (432/586) with PDS. NACT use increased significantly from 22% (56/256) before 2010 (at which point the results of the randomized trial

* Corresponding author at: Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States. zivanovo@mskcc.org (O. Zivanovic).

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ygyno.2016.01.008>.

were published) to 30% (98/330) after 2010 ($p = 0.037$). Although patients who underwent PDS were more likely to experience grade 3/4 surgical complications than those who underwent NACT, those selected for PDS had a median OS of 71.7 months (CI, 59.8-not reached) compared with 42.9 months (CI 37.1-56.3) for those selected for NACT.

Conclusions—In this single-institution analysis, the best survival outcomes were observed in patients who were deemed eligible for PDS followed by platinum-based chemotherapy. Selection criteria for NACT require further definition and should take institutional surgical strategy into account.

Keywords

Advanced-stage ovarian cancer; Neoadjuvant chemotherapy; Overall survival; Progression-free survival; Primary debulking surgery; Interval debulking surgery

1. Introduction

In 2015, an estimated 21,290 women will be diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer in the United States; and approximately 14,180 women will die from this disease. The vast majority of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer will present with advanced malignancy, with stage III or IV disease [1]. Currently, there are no adequate screening methods to detect or prevent ovarian cancer in the general population; the use of CA-125 and pelvic ultrasonography in asymptomatic women have not resulted in a decrease in mortality in the general population [2]. Standard treatment in advanced-stage disease includes primary debulking surgery (PDS) followed by a platinum- and taxane-containing chemotherapy regimen, with consideration of neoadjuvant chemotherapy (NACT) in patients who are poor surgical candidates or have unresectable disease [3,4].

Several studies have demonstrated survival after NACT approximates that of upfront suboptimal PDS [5–8]. Included in this research effort is a collaborative study of the European Organization for Research and Treatment of Cancer–Gynecological Cancer Group (EORTC–GCG) and National Cancer Institute of Canada Clinical Trials Group (NCIC–CTG). The trial randomized 718 women with bulky stage III or stage IV advanced ovarian cancer to PDS or NACT followed by interval debulking surgery (IDS) and incorporated survival, recurrence, and quality of life endpoints. Median progression-free survival (PFS) was 12 months for both the PDS and NACT groups, and median overall survival (OS) was 29 months and 30 months for the PDS and NACT groups, respectively. The authors concluded that NACT with IDS is not inferior to PDS [9,10]. The Chemotherapy OR Upfront Surgery (CHORUS) trial is another recently published non-inferiority trial randomizing patients to either NACT or PDS. The study confirmed similar oncologic outcomes in both patient cohorts. Despite the similar PFS and OS between NACT and PDS in the study arms, both trials showed much lower than expected survivals following PDS compared with survival outcomes of other studies. Median PFS was 12 and 11 months and median OS was 29 and 23 months in the EORTC and CHORUS trials, respectively [11–13].

In a survey of members of the Society of Gynecologic Oncology (SGO) conducted prior to the publication of the EORTC/NCIC trial results, 60% of respondents stated they were using NACT in only a minority (10%) of their advanced-stage ovarian cancer cases and 82% did not consider the available evidence sufficient to alter their practice [14]. Contemporary data and meta-analyses suggest that a complete gross tumor resection without any visible residual disease is associated with the best outcomes, and many now believe that NACT should be used in patients in whom a complete gross resection at PDS is unlikely, including patients who have minimal (less than 1 cm) residual disease. At our institution, PDS has been the preferred treatment strategy for patients with advanced ovarian cancer, including those requiring radical peritonectomy and upper abdominal procedures, and NACT has been used for patients with significant comorbidities not deemed fit for complex surgery.

We hypothesized the EORTC/NCIC trial results and the benchmark for complete gross resection at the time of debulking surgery has impacted our practice patterns, resulting in an increase in NACT as a primary treatment strategy. We sought to identify how NACT patient selection criteria and rates of optimal surgical resection at the time of interval and primary surgery have changed over a time period during which the EORTC/NCIC trial results were published.

2. Methods

An institutional review board (IRB)-approved retrospective analysis at Memorial Sloan Kettering Cancer Center was performed. We reviewed all consecutive patients with a diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer treated at our institution from January 1, 2008 to May 1, 2013, which encompassed a 32-month period before and 32-month period after results from the EORTC/NCIC trial were published on September 3, 2010 (our study midpoint).

We included all newly diagnosed patients who presented at our institution with stage III or IV disease according to 1988 International Federation of Gynecology and Obstetrics (FIGO) staging criteria [15]. All cases were reviewed by a specialized gynecologic pathologist to confirm histology, which included any grade 2 or 3 serous, mucinous, clear cell, anaplastic, undifferentiated, or endometrioid subtype. Patients were excluded if they had already undergone PDS at an outside facility, completed NACT prior to presentation, presented with borderline or low-grade histology, or had stage I or II disease. Chemotherapy in the adjuvant and neoadjuvant setting included platinum- and taxane-based regimens and reflected standard treatment protocols for the time period. Our institution was then enrolling patients on Gynecologic Oncology Group (GOG) trials 218, 252, 262 and 9923, which incorporated bevacizumab or veliparib treatment [16]. The decision to offer PDS as a primary treatment strategy was at the discretion of the individual surgical attending. The shared philosophy in our department during the time was to surgically manage advanced ovarian cancer with intent for optimal (< 1 cm) cytoreduction and a goal of complete cytoreduction as deemed appropriate by the attending surgeon. Debulking procedures involved standard hysterectomy, oophorectomy, omentectomy with or without gastrointestinal surgery, and radical upper abdominal procedures such as diaphragm resection, splenectomy, distal

pancreatectomy, and liver resection, if appropriate and necessary to achieve optimal cytoreduction.

Patients were considered to have undergone PDS if any open surgery was performed with intent to perform a debulking procedure. Patients were defined as NACT cases if diagnostic laparoscopy was performed with the purpose of evaluation for resectability. During this time period, our institution used laparoscopy as an adjunct for treatment selection to NACT or PDS without a formal scoring system. Patients who had undergone a surgical procedure for a different indication (i.e., appendicitis, cholecystitis, bowel obstruction) either at our institution or prior to their consultation and malignancy was discovered at the time of surgery were considered NACT cases. Patients who achieved complete gross resection were those in whom no visible residual disease remained after surgical debulking. Patients were considered optimally debulked if they had no visible residual disease larger than 1 cm in greatest dimension after surgery. Patients were considered suboptimally debulked if they had any residual disease larger than 1 cm in greatest dimension after surgery. The date of diagnosis was defined as the date of surgery or date of first pathologic confirmation of malignancy, obtained via pleural/peritoneal fluid, fine needle aspirate, or core biopsy of solid tumor. Recurrence was defined as the time from date of diagnosis to the first radiographic evidence of progression even if a rise in CA-125 superseded radiographic evidence of progression. Surviving patients were censored at the date of last contact.

All clinical variables were collected from the medical records and tested for association with PDS and NACT. These variables include body mass index (BMI), serum albumin and CA-125, documented comorbidities, prior surgeries, and the presence of carcinomatosis on computed tomography (CT) scan. Adverse events were captured using our institutional morbidity and mortality data, which are prospectively collected and reviewed on a quarterly basis within our department [17].

2.1. Statistical analysis

The associations between clinical factors and the time periods were tested either using the Fisher Exact test for categorical variables or Wilcoxon Rank Sum test for continuous variables. PFS was defined from the diagnosis date (surgery date for PDS and biopsy date for NACT) to the progression date or death date or last follow-up date. OS was defined from the diagnosis date to the death date or last follow-up date. The median survival and the survival rate were obtained using Kaplan–Meier methodology. Survival in individual NACT subgroups when categorized by residual disease status was calculated using the landmark method in order to incorporate the time-dependent nature of the interval debulking outcome. The landmark method at 12 weeks after the diagnosis date was used. All analyses were performed in SAS 9.4.

3. Results

Five hundred eighty-six patients were evaluated over the study period. The median age was 62 years (range, 30–90 years) and median BMI was 26.1 kg/m² (range, 15.9–57.5 kg/m²). There were 406 (69%) patients with stage III disease, and 570 (97%) had disease of serous histology. One hundred fifty-four (26%) of 586 patients were treated with NACT and 432

(74%) of 586 were treated with PDS. The median ages were 62 years and 65 years for patients selected for PDS and NACT, respectively ($p = 0.01$). Median preoperative CA-125 was 460 units/mL in the PDS group compared with 830 units/mL in the NACT group ($p = 0.01$). Preoperative serum albumin was 4.1 in the PDS group compared with 3.9 in the NACT group ($p = 0.001$). Preoperative carcinomatosis was evident on CT scan in 72% of patients in the PDS group and 86% of patients in the NACT group ($p = 0.001$). Twenty-five percent of patients in the PDS group compared with 48% in the NACT group had FIGO stage IV disease ($p = 0.001$). Patient characteristics for the entire cohort are listed in Table 1. Patient characteristics grouped by treatment strategy for the entire cohort are listed in Table 2.

NACT use increased across the two time periods from 22% (56 of 256 patients) before 2010 (at which time the EORTC/NCIC trial results were published) to 30% (98 of 330 patients) after 2010 ($p = 0.037$). The median number of NACT cycles administered was 4 (range, 1–7). Before 2010, stage and comorbidities, namely diabetes, were associated with the selection of NACT over PDS. After 2010, there were a greater number of variables associated with NACT-over-PDS selection: older age, stage IV disease, pulmonary disease, lower median preoperative albumin, higher median preoperative CA-125, and the presence of carcinomatosis on preoperative CT imaging. Table 3 outlines factors associated with NACT treatment in both time periods. For the 154 patients who received NACT over the entire study period, four basic indications were recorded in the medical records: clinical judgment (i.e., radiographic imaging, failure to clear for surgery, performance status, and medical comorbidities), 109 (71%); unresectable disease based upon laparoscopic evaluation, 20 (13%); stage IV disease confirmed via video-assisted thoracoscopic surgery, 11 (7%); and pulmonary embolus at the time of diagnosis, 14 (9%).

3.1. Residual disease

In patients who underwent PDS, 351 (81%) of 432 patients were optimally debulked, 203 (47%) achieved a complete gross resection, and 81 (19%) were suboptimally debulked. Before 2010, 162 (81%) of 200 PDS patients were optimally debulked, 85 (43%) achieved a complete gross resection, and 38 (19%) were suboptimally debulked. After 2010, 189 (81%) of 232 PDS patients were optimally debulked, 118 (51%) achieved a complete gross resection, and 43 (19%) were suboptimally debulked ($p = 0.17$). In the total cohort, 427 (99%) of 432 patients received chemotherapy after PDS.

In patients who underwent NACT, 149 (97%) went on to have an IDS: 131 (88%) of 149 patients were optimally debulked, 82 (55%) achieved a complete gross resection, and 18 (12%) were suboptimally debulked. Before 2010, 50 (91%) of 55 NACT patients were optimally debulked, 29 (53%) achieved a complete gross resection, and 5 (9%) were suboptimally debulked. After 2010, 81 (86%) of 94 patients were optimally debulked, 53 (56%) achieved a complete gross resection, and 13 (14%) were suboptimally debulked.

When comparing the two time periods, there was no significant difference in resection results among patients undergoing PDS ($p = 0.17$) or NACT ($p = 0.51$). Table 4 outlines the resection rates for PDS and NACT by time period.

3.2. Adverse events

There were no 30-day postoperative deaths (grade 5 events) in either the PDS or NACT cohort across both time periods. There were 80 (14%) grade 3 or 4 adverse events in the entire cohort of 586 patients; 71 (16%) among the 432 patients in the PDS group and 9 (6%) among the 154 patients in the NACT group ($p < 0.001$). Before 2010, there were 38 events (19%) among the 200 patients in the PDS group and 3 (5%) among the 56 patients in the NACT group ($p = 0.013$). After 2010, there were 33 events (14%) among the 232 patients in the PDS group and 6 (6%) among the 98 patients in the NACT group ($p = 0.04$).

3.3. Survival

Median follow-up for the 357 surviving patients was 44.4 months (range, 1.3–90.3 months). Median follow-up was 66.8 months (range, 1.3–90.3 months) for patients treated before 2010 and 37.8 months (range, 6.8–57.8 months) for patients treated after 2010. The median PFS was 19.1 months (95% CI, 17.8–21) for all patients. The median OS was 63.2 months (95% CI, 55.3–73.2) for all patients.

The median PFS and OS for patients who underwent PDS were 21.7 months (95% CI, 19.5–23.8) and 71.7 months (95% CI, 59.8–not reached), respectively. The median PFS and OS for patients selected for NACT were 13.9 months (95% CI 12.5–16.1) and 42.9 months (95% CI, 37.1–56.3), respectively.

Median PFS and OS stratified by residual disease at the time of primary and interval debulking surgery are summarized in Table 5 and presented as Kaplan–Meier curves in Fig. 1.

4. Discussion

We observed an increase in the selection of NACT as a primary treatment strategy for advanced-stage ovarian cancer in the time period following the publication of the EORTC/NCIC trial results, which showed non-inferiority of NACT compared with PDS; however, the majority of patients (70%) still undergo PDS as their primary treatment strategy. This increase is multi-factorial; during this time period, the use of radiographic imaging criteria and select clinical parameters were in practice based on emerging efforts across the country to formalize selection criteria [18], and the EORTC/NCIC trial results were being discussed even prior to publication at national meetings. Prospective data supporting NACT as a safe alternative combined with an increased effort to better select patients for PDS likely reflect this rise in NACT within our institution.

Survival outcomes in the NACT arms of the EORTC and CHORUS trials were similar to those in our study. Median PFS and OS for patients who underwent NACT in our study were 14 and 43 months, respectively, compared with 12 and 30 months in the EORTC/NCIC trial and 12 and 24 months in the CHORUS trial, respectively. In our study, patients offered NACT were older with a greater proportion of stage IV disease, had higher preoperative CA-125, lower preoperative serum albumin, and more widespread disease compared with women offered PDS. Despite the differences seen in each treatment group, the increasing NACT use in our study did not significantly impact optimal cytoreduction

rates. It is also worth noting in our cohort that all but 5 of the patients given NACT went on to have an IDS, which may be a higher rate than that of other published cohorts. The complete gross resection rate increased from 43% to 51% in our PDS group after selecting more patients for NACT, likely as a result of the increased selection of patients with advanced age and stage to receive NACT. Given the survival difference between those who achieve a complete gross resection at PDS compared with a complete gross resection at IDS, residual disease at time of surgery may not be a valid endpoint to cross-compare and warrants further investigation.

The EORTC/NCIC and CHORUS trials each showed similar survival between treatment groups but with improved optimal resection rates and less adverse events in their NACT treatment arms, leading the authors to conclude that NACT is a reasonable treatment strategy for advanced ovarian cancer [9,19]. Survival and resection data for the PDS group in our study contrasts sharply with that of the EORTC/NCIC and CHORUS trials. In our study, PDS patients had optimal resection rates of 80–81%, with a PFS of 21 months and an OS of 72 months. It is likely that this difference is attributable to our case selection for PDS using previously reported criteria [18], the selection of patients with predominantly poor prognosis randomized in the EORTC/NCIC and CHORUS trials, or a combination of both factors.

NACT is gaining in popularity, yet cytoreductive surgery followed by chemotherapy remains the accepted standard in the primary management of patients with advanced-stage ovarian cancer, with superior survival advantage for patients who undergo optimal cytoreductive surgery followed by combined intravenous/intraperitoneal (IV/IP) chemotherapy [12,20,21]. Patients presenting with bulky disease in the upper abdomen often require extensive procedures to achieve optimal resection, including the removal of spleen, pancreas, and portions of liver and diaphragm, and there is an increased risk for suboptimal cytoreduction and perioperative complications [22–24]. Our dataset confirms that PDS is associated with more grade 3 and 4 30-day surgical complications when compared with NACT after IDS. However, we did not observe any perioperative deaths in either group, and the incidence of severe adverse events was lower in both the PDS and NACT cohorts compared with the CHORUS trial.

The best survival outcomes in our study were observed in patients who achieved a complete gross resection at the time of PDS, although OS after complete gross resection at the time of IDS (median OS, 66 months) was comparable to that for patients left with minimal residual disease at PDS. It is clear that selection bias is involved, as older and more advanced-stage patients with more tumor burden are selected for NACT; however, it is important to note that even in patients who respond favorably to NACT and undergo a complete gross tumor resection after NACT, we do not observe better outcomes than in patients who have minimal residual disease after PDS. While this may be a function of poor tumor biology, it may also be a result of treatment delay and treatment interruption when performing interval surgery, which could have a negative effect on tumor growth kinetics and the development of chemotherapy resistance. Future studies should evaluate whether timing, frequency, route of administration and number of cycles of NACT to administer before and after IDS can optimize outcomes [33].

Identifying patients at highest risk for suboptimal cytoreductive surgery is of paramount importance to maximize survival and quality of life outcomes for patients [25,26]. The predictive utility of preoperative variables including CA-125, CT scan, age, stage, comorbid conditions, and a host of other factors that can predict success or failure in the operating room have been examined. Staging laparoscopy has gained popularity after Fagotti et al. published their laparoscopic scoring system, termed the predictive index value, which is based on location of disease in the pelvis and mid and upper abdomen [27]. Nick et al. recently published the MD Anderson Algorithm, which incorporates staging laparoscopy using 'the Fagotti score' coupled with intraoperative surgeon consensus for resectability. This practice change has resulted in improved rates of complete resection, with a notable 100% consensus among surgeons [28]. Suidan et al. [29] published results combining Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center preoperative CT and clinical data to generate a preoperative index score for surgical debulking feasibility in advanced ovarian cancer. These results utilize nine radiologic and serologic criteria within a constructed predictive model, with a predictive accuracy of 76%. Based upon this work, our current treatment algorithm incorporates age, American Society of Anesthesiologists (ASA) status, stage at presentation, and key CT imaging features to serve as a guideline to effectively select patients for NACT (Supplementary Figs. 1 and 2; Supplementary Table 1).

Our study is limited by its retrospective design. We did not include detailed neoadjuvant and adjuvant chemotherapy treatment information in our analysis. This is important when considering why PFS and OS rates do not appear substantially different across time periods for either the NACT or PDS group treated after 2010 (data not shown). It is possible that variation in treatment regimen impacted survival. The Japanese Gynecologic Oncology Group (JGOG) trial 3016 randomized women with advanced ovarian cancer to carboplatin and paclitaxel every 3 weeks versus carboplatin with weekly paclitaxel in the adjuvant setting. Their data showed an improved PFS in the weekly paclitaxel arm, and in a subgroup analysis, this benefit was greater for women who underwent suboptimal cytoreductive surgery [30]. Tiersten et al. published results of a phase II analysis examining NACT with IDS followed by IP chemotherapy in advanced ovarian cancer. In the trial, the authors reported a median PFS of 21 months and median OS of 32 months in their entire cohort compared with a PFS of 29 months and OS of 34 months for patients who ultimately received IP chemotherapy [31]. Suidan et al. [32] retrospectively compared patients receiving primary IV/IP chemotherapy after optimal PDS with those receiving consolidation IP chemotherapy after PDS spanning 2005–2011. Their results show an improved OS in the primary IV/IP cohort, from 57.5 months using the consolidation regimen to 78.8 months. Considering these data, it is possible that variations in treatment, including weekly paclitaxel or IP treatment regimens, could impact survival rates in either treatment group. Eighty-three patients (14%) in our PDS study arm were enrolled on GOG trials 218, 252, 262, or 9923. These were clinical trials enrolling women with advanced ovarian cancer that included non-standard chemotherapy, bevacizumab or veliparib, as part of the treatment arms. Future analyses will incorporate duration and regimen of choice for neoadjuvant and adjuvant treatment to better understand chemotherapy's impact on surgical resectability and survival.

In our study, patients who received NACT represent a prognostically poorer group with respect to performance or disease status and comparable outcomes to those of the phase III

randomized trials evaluating NACT versus PDS. On the other hand, patients selected for PDS at our institution experienced clinically relevant discrepancies in resection rates and improved survival outcomes compared with those of published randomized trials. This selection bias limits a direct comparison with the two prospective, randomized trials that support comparable outcomes between PDS and NACT. Many argue that complete gross resection is the best threshold for selecting patients for PDS, and if unable to achieve this, NACT is a reasonable alternative. Although complete gross resection is the goal, our retrospective results suggest attaining visible residual disease to 1 cm at the time of PDS may continue to be a worthwhile surgical resection goal, as it offers a comparable PFS and OS compared with NACT followed by complete gross interval cytoreductive surgery. The available prospective evidence suggests NACT to be safer than PDS, with similar outcomes in patients with advanced-stage ovarian carcinoma, but it is not clear whether these findings are generalizable to all patients with advanced ovarian cancer, or whether this is true predominantly for those patients with unresectable disease, poor performance and poor nutritional status. Before further increasing the use of NACT to reduce perioperative morbidity, we must demonstrate that NACT offers the same, or better, outcomes in high-volume centers with experience in cytoreductive surgery. At the same time, we have to refine and improve selection criteria to minimize the number of patients who are selected for PDS but do not benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- NACT utilization has increased as an alternative to PDS in select patients.
- Optimal (<1 cm) PDS affords advanced ovarian cancer patients the greatest survival advantage.
- If not eligible for PDS, patients benefit most from complete gross resection at IDS.

Fig. 1.
 A. Overall Survival by Primary Debulking Surgery Residual Disease (PDS Cohort); B.
 Overall Survival by Interval Debulking Surgery Residual Disease (NACT Cohort, landmark
 method).

Table 1

Overall patient characteristics (N = 586).

Characteristic	No.	%
Age, years		
Median	62	
Range	30–90	
BMI, kg/m ²		
Median	26.1	
Range	15.9–57.5	
Preoperative CA-125, units/mL		
Median	500.3	
Range	3–32,100	
Preoperative albumin		
Median	4.1	
Range	1.4–5	
Preoperative carcinomatosis on CT	438	75
Presence of comorbidity		
Hypertension	209	36
Diabetes	47	8
Pulmonary	73	12
Coronary Artery Disease	24	4
Stroke	7	1
Congestive Heart Failure	3	0.5
Renal	12	2
Hypothyroid	90	15
Hyperthyroid	12	2
Dementia	2	0.3
Hepatic	12	2
Peripheral vascular disease	8	1
Prior laparotomies		
0	368	63
1	150	26
2	49	8
3 or greater	19	3
Histology		
Serous	570	97
Other	16	3
FIGO Stage		
III	406	69
IV	180	31
Origin		
Ovary	413	70

Characteristic	No.	%
Fallopian tube	130	22
Peritoneal	43	7
NACT ^a	154	26

p values were obtained using the Fisher Exact test for categorical variables and Wilcoxon Rank Sum test for continuous variables

CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; NACT, neoadjuvant chemotherapy

^a 8 patients were included who received 1 cycle of NACT prior to consultation in cases where the surgeon evaluating the patient at our institution agreed this was the optimal management plan.

Table 2

Patient characteristics by treatment arm: PDS (N = 432) versus NACT (N = 154).

Characteristic	PDS		NACT		p
	No.	%	No.	%	
Age, years					
Median	62		65		0.01
Range	30–86		34–90		
BMI, kg/m ²					
Median	26.3		25.7		0.56
Range	15.9–57.5		17.4–49.8		
Preoperative CA-125, units/mL					
Median	460		830		0.01
Range	3–24,500		6–32,100		
Preoperative albumin					
Median	4.1		3.9		0.001
Range	1.4–5		1.7–4.8		
Preoperative carcinomatosis on CT	305	72	133	86	<0.001
Presence of comorbidity					
Hypertension	151	35	58	38	0.55
Diabetes	32	7	15	10	0.38
Pulmonary	45	10	28	18	0.01
Coronary Artery Disease	17	4	7	5	0.81
Stroke	4	1	3	2	0.38
Congestive Heart Failure	2	0.5	1	0.6	1
Renal	10	2	2	1	0.74
Hypothyroid	69	16	21	14	0.51
Hyperthyroid	11	3	1	0.6	0.19
Dementia	2	0.5	0	0	1
Hepatic	9	2	3	2	1
Peripheral Vascular Disease	5	1	3	2	0.43
Prior Laparotomies					
0	275	64	93	60	0.65
1	105	24	45	29	
2	38	9	11	7	
3 or more	14	3	5	3	
Histology					
Serous	418	97	152	99	0.26
Other	14	3	2	1	
FIGO Stage					
III	326	75	80	52	<0.001
IV	106	25	74	48	
Origin					

Characteristic	PDS		NACT		p
	No.	%	No.	%	
Ovary	292	68	121	79	0.004
Fallopian Tube	110	25	20	13	
Peritoneal	30	7	13	8	
30-day postoperative adverse events					<0.001
Grade 3 or 4	71	16	9	6	
Grade 5	0	0	0	0	

30-day postoperative adverse events are graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; BMI, body mass index; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics.

Table 3

Factors associated with the use of NACT before and after 2010.

Characteristic	Before 2010				After 2010			
	PDS (N = 200)		NACT (N = 56)		PDS (N = 232)		NACT (N = 98)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	61.7		65.4		62.4		66.1	
Range	30.2–86.2		36.4–83.3		35.4–86.7		34.1–90.9	
BMI, kg/m ²								
Median	26.1		26.4		26.3		25.3	
Range	15.9–54.6		17.5–44		17.2–57.5		17.4–49.8	
Preoperative CA-125, units/mL								
Median	442		387		526.3		1098.5	
Range	3–24,500		12–10,500		7–16,519		6–32,100	
Preoperative albumin								
Median	4.1		4.1		4.1		3.9	
Range	2–5		2.7–4.8		1.4–5		1.7–4.8	
Preoperative carcinosarcoma on CT	150	75	46	82	155	68	87	89
Presence of comorbidity								
Hypertension	73	37	28	50	78	34	30	31
Diabetes	12	6	9	16	20	9	6	6
Pulmonary	17	9	6	11	28	12	22	22
Renal	8	4	2	4	2	1	0	0
Prior laparotomies								
0	139	70	33	59	136	59	60	61
1	41	21	18	32	64	28	27	28
2	14	7	2	4	24	10	9	9
3 or greater	6	3	3	5	8	3	2	2
FIGO stage								
III	153	77	31	55	173	75	49	50
IV	47	23	25	45	59	25	49	50

p values are obtained using Fisher Exact test for categorical variables and using Wilcoxon Rank Sum test for continuous variables.

Table 4

Resection rates for PDS and NACT by time period.

	<u>Before 2010</u>		<u>After 2010</u>		p
	No.	%	No.	%	
<i>PDS</i>					
Complete gross resection	85	43	118	51	0.17
Optimal visible residual (≤ 1 cm)	77	39	71	31	
Suboptimal (>1 cm)	38	19	43	19	
<i>NACT</i>					
Complete gross resection	29	52.7	53	56.4	0.51
Optimal visible residual (≤ 1 cm)	21	38.2	28	29.8	
Suboptimal (>1 cm)	5	9.1	13	13.8	

p values are obtained using the Fisher Exact test for categorical variables and Wilcoxon Rank Sum test for continuous variables.

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

Table 5

Survival outcomes in patients who underwent NACT (N = 154) and PDS (N = 432) stratified by residual disease.

	PFS		OS	
	Median (months)	95% CI (months)	Median (months)	95% CI (months)
<i>PDS</i>				
Complete gross resection	29.1	24.9–36	Not reached	
Optimal visible residual (≤ 1 cm)	19.1	15.8–21.7	65.6	51.8–not reached
Suboptimal (>1 cm)	15.9	11.9–18.2	49.7	36.6–55.3
<i>NACT^a</i>				
Complete gross resection	16.4	11.5–20.2	66.6	36.6–not reached
Optimal visible residual (≤ 1 cm)	9.8	8.4–11.6	39.7	31–53.6
Suboptimal (>1 cm)	7.4	5.7–11.4	28.4	15.8–47.5

p values were obtained using the Fisher Exact test for categorical variables and Wilcoxon Rank Sum test for continuous variables.

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

^aThe median PFS and OS reported for patients who received NACT was obtained using the landmark method to account for the interval debulking status. See methods section.