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DELAYS FROM NEOADJUVANT CHEMOTHERAPY TO INTERVAL DEBULKING SURGERY AND SURVIVAL IN OVARIAN CANCER

Ying L Liu¹, Qin C Zhou², Alexia Iasonos², Olga T Filippova³, Dennis S Chi³, Oliver Zivanovic³, Yukio Sonoda³, Ginger Gardner³, Vance Broach³, Roisin OCearbhaill¹, Jason A Konner¹, Carol A Aghajanian¹, Kara Long³, William Tew¹

¹Gynecologic Medical Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

²Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

³Gynecologic Oncology, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Abstract

Introduction: Delays from primary surgery to chemotherapy are associated with worse survival in ovarian cancer; however, the impact of delays from neoadjuvant chemotherapy to interval debulking surgery is unknown. We sought to evaluate the association of delays from neoadjuvant chemotherapy to interval debulking with survival.

Methods: Patients with a diagnosis of stage III/IV ovarian cancer receiving neoadjuvant chemotherapy from July 2015 to December 2017 were included in our analysis. Delays from neoadjuvant chemotherapy to interval debulking were defined as time from last preoperative carboplatin to interval debulking >6 weeks. Fisher's exact/Wilcoxon rank sum tests were used to compare clinical characteristics. Kaplan-Meier method, log-rank test and multivariate Cox Proportional-Hazards models were used to estimate progression-free and overall survival and examine differences by delay groups, adjusting for covariates.

Results: Of the 224 women, 159 (71%) underwent interval debulking and 34 (21%) of these experienced delays from neoadjuvant chemotherapy to interval debulking. These women were older (median 68 vs. 65 years, $p=0.05$) and received more preoperative chemotherapy cycles (median 6 vs. 4, $p=0.003$). Delays from neoadjuvant chemotherapy to interval debulking were associated with worse overall survival (HR 2.4 95% CI 1.2–4.8, $p=0.01$); however, survival was

Corresponding Author: Dr William Tew, Gynecologic Medical Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, teww@mskcc.org.

AUTHOR CONTRIBUTIONS

Conception and design: YL, WT, KL, CA

Acquisition, analysis, interpretation of data: YL, OF, QZ, AI

Statistical analysis: QZ, AI

Administrative, technical, material support: OF

Supervision: WT, CA, KL

Drafting of manuscript: YL, WT, KL, CA

Critical revision of manuscript (all authors)

Final approval of manuscript (all authors)

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not significantly shortened after adjusting for age, stage and complete gross resection, HR 1.66 95% CI 0.8–3.4, $p=0.17$. Delays from neoadjuvant chemotherapy to interval debulking were not associated with worse progression-free survival (HR 1.55 95% CI 0.97–2.5, $p=0.062$). Increase in number of preoperative cycles ($p=0.005$) and lack of complete gross resection ($p<0.001$) were the only variables predictive of worse progression-free survival.

Discussion: Delays from neoadjuvant chemotherapy to interval debulking were not associated with worse overall survival after adjustment for age, stage and complete gross resection.

INTRODUCTION

Many studies have examined the time interval from primary debulking surgery to postoperative chemotherapy and have shown that delays greater than 6 weeks are associated with worse survival^{1,2}. In one analysis, if the time to initiation of chemotherapy exceeded 25 days after primary debulking surgery, there was an increased risk of death.³ However, few studies have examined the impact of delays from neoadjuvant chemotherapy to interval debulking surgery. Given the increasing use of neoadjuvant chemotherapy in treating women with advanced ovarian cancer over the last decade, we consider this an important question to address.^{4,5,6}

A few small studies suggest that delays, from neoadjuvant chemotherapy to interval debulking may affect survival. Le et al. found that in 97 women receiving neoadjuvant chemotherapy, increased time between neoadjuvant chemotherapy and surgery may adversely affect overall survival, but this association was only significant in women with sub-optimal debulking.⁷ Chen et al. studied 152 women with stage III/IV ovarian cancer and found that time from neoadjuvant chemotherapy to interval debulking >4 weeks predicted worse progression-free but not overall survival.⁸

In addition, there are multiple circumstances for delays during neoadjuvant therapy, including delays from diagnosis to chemotherapy, chemotherapy to interval debulking, and surgery to postoperative chemotherapy. Lee et al. studied 220 women with newly diagnosed ovarian cancer receiving neoadjuvant therapy and found that the time interval between neoadjuvant and postoperative chemotherapy affected survival, and that longer time intervals resulted in poorer survival.⁹

Some hypothesize that delays in neoadjuvant chemotherapy are due to underlying patient comorbidity that may adversely influence surgical and survival outcomes.^{2,10} Although some studies have reported that delays in chemotherapy after primary debulking were more likely to occur in the older adult, the malnourished, and those with high Charlson comorbidity index scores², others have found that comorbidity and systems delays may affect survival independently.¹⁰

As a result, it is unclear if delays in neoadjuvant therapy have an independent impact on outcomes, or if all associations are mediated through increased patient comorbidity and suboptimal surgeries. Given this, we sought to evaluate the association of delays from neoadjuvant chemotherapy to interval debulking with survival, adjusting for other clinical variables as well as other time intervals in therapy.

METHODS

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center, protocol 17–430.

Patient Selection

From July 2015 until December 1, 2017, we identified 241 women with newly diagnosed, pathologically verified ovarian, fallopian tube or primary peritoneal cancer and were recommended to receive neoadjuvant chemotherapy. Patients were identified from a retrospectively kept institutional ovarian database, which was started on July 1, 2015, and captures all women presenting to Memorial Sloan Kettering Cancer Center with an adnexal complaint. Women were subsequently excluded if they were still undergoing treatment at the end of data abstraction (n=4), had incomplete chemotherapy data (n=8) or a histology revealing germ cell (n=1), small cell (n=3) or mucinous adenocarcinoma (n=1), resulting in 224 women who were included in this study. Of these, 162 women underwent debulking surgery of which 159 had complete chemotherapy dates and were included in this analysis. (Figure S1).

Data Collection

Clinical data were abstracted and verified from the electronic medical record for these patients from July 1, 2018 to December 1, 2018 by two independent reviewers (YL and OF). Patients were identified via the center's Ovarian Database, which tracks all patients seen with an ovarian complaint from the time of initial visit. Age was defined in years from the date of pathological diagnosis. Stage was defined at pathological diagnosis using the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging.¹¹ The Charlson comorbidity score (a composite score measuring comorbidity in 12 areas, which has been shown to be predictive of mortality)^{12,13} was calculated based on medical conditions present at pathological diagnosis. CA125 levels, serum albumin levels, and Karnofsky performance score¹⁴ were collected at the time of first chemotherapy treatment from the medical record. Body mass index, calculated as weight (kg) divided by height² (m²), was collected at the time of first chemotherapy. *BRCA* testing status and results were abstracted from the medical record.

Surgical and medical oncology notes were reviewed to determine the indication for neoadjuvant therapy and were categorized as follows: 1) extent of disease not amenable to surgery either by a predictive model¹⁵ or by radiologic evidence of stage IV disease; 2) patient comorbidity preventing surgery; 3) both extent of disease and patient comorbidity; 4) other, which was mostly due to venous thromboembolic disease. Optimal debulking was defined as residual disease <1cm. A complete gross resection was defined as no visible residual disease at the conclusion of surgery.

Chemotherapy regimens/doses were documented. Institutional practice guidelines allow for an individualized decision between weekly or every 3 week administration of neoadjuvant chemotherapy. Dose reductions were defined as any reductions in chemotherapy occurring before debulking surgery and included any of the following: 1) carboplatin area under the

curve (AUC) <5 ; 2) weekly paclitaxel <80 mg/m²; 3) every 3-week paclitaxel <175 mg/m²; 4) any single-agent treatment for one or more treatment cycles. These were further categorized as baseline dose reductions or dose reductions occurring after the first cycle but before surgery. The use of bevacizumab (monotherapy or combined with other chemotherapy) and PARP inhibitors at any time during treatment was documented. at any time during treatment was documented.

Defining Neoadjuvant Time Intervals

T_{NACT} was defined as the time from pathological diagnosis to the start of chemotherapy. The period from the last preoperative carboplatin treatment to the first postoperative chemotherapy treatment was divided into two time periods: a. the time from last preoperative carboplatin to interval debulking; and b. time from interval debulking to first post-operative chemotherapy (Figure 1). Delay was defined as time from last preoperative carboplatin to interval debulking >6 weeks, based on the EORTC study.⁶ In patients with delays in time from last preoperative carboplatin to interval debulking, detailed chart review was performed to determine the reason(s) for delays.

Statistical Analysis

Summary statistics were used to define each of the neoadjuvant time intervals. Fisher's exact and Wilcoxon rank sum tests were used to compare clinical characteristics based on delays in time from last preoperative carboplatin to interval debulking. Progression-free survival was derived from date of surgery to date of disease progression, defined as clinical recurrence via pathologically confirmed biopsy (when available) or imaging showing disease recurrence per the clinical provider, or death in patients without recurrence, or last follow-up in those without recurrence or death. Overall survival was derived from date of interval debulking to date of death from all causes, or last follow-up in those without death. The Kaplan-Meier method was used to estimate median survival and the survival rate at 1 year. The log-rank test and Cox Proportional-Hazards (CoxPH) model were used to assess the relationship of covariates to outcome. Landmark analysis was used for the time-dependent variable time from interval debulking to first post-operative chemotherapy, and only patients who received postoperative treatments were included in these analyses.

RESULTS

Patient Characteristics

Median age of the cohort was 66 years (range; 43–87), and most patients had high-grade serous ovarian cancer (96%). Most had stage IV disease (69%) and were referred for neoadjuvant therapy due to extent of disease (70%). Twenty-eight women (18%) had *BRCA* 1/2 mutations, but 30 had not yet undergone testing. Median body mass index was 25.5 kg/m², (range; 15.4–60.1), and median CA125 level was 1170 U/mL (range; 4–38,600). At start of chemotherapy, median Karnofsky performance score was 80% (range; 50–100%), Charlson score was 8 (range; 6–12), and albumin was 3.8 g/dL (range; 2.3–4.9). Most women received weekly paclitaxel and carboplatin (76%), and only 11% required a dose reduction. Patients received a median of 4 preoperative cycles (range; 2–7); 90% of patients received postoperative chemotherapy, with a median of 3 postoperative cycles

(range; 1–8). In addition to chemotherapy, 8 women received bevacizumab, and 14 received PARP inhibitor or placebo on protocol. Of the 159 women, 139 (87%) underwent optimal debulking and 106 (67%) achieved complete gross resection (Table 1).

Neoadjuvant Time Intervals and Delays

Time from last preoperative carboplatin to interval debulking ranged from 15–139 days, with a median of 34 days and mean of 36.9 days. Time from pathological diagnosis to preoperative chemotherapy ranged from 2–92 days, with a median of 19 and mean of 22.3 days. In those who were diagnosed at Memorial Sloan Kettering (n=69, 43%), the time from pathological diagnosis to preoperative chemotherapy was significantly shorter ($p<0.001$) with a median of 10 days (range; 2–37) compared to a median of 26 days (range; 2–92) in those diagnosed elsewhere (n=90, 57%). The period from the last preoperative carboplatin treatment to the first postoperative chemotherapy treatment ranged from 26–150 days, with a median of 64 and mean of 67.5 days. The time from interval debulking to first post-operative chemotherapy ranged from 13–87 days, with a median of 31 and mean of 33.4 days.

Of the 159 women who received neoadjuvant chemotherapy and underwent interval debulking, 34 (21%) had delays in time from neoadjuvant chemotherapy to interval debulking. In those with delays, median time from neoadjuvant chemotherapy to interval debulking was 48 days (range; 43–139) compared to a median of 32 days (range; 15–42) in those without delays. Patients with delays from neoadjuvant chemotherapy to interval debulking were older (median age 67.5 vs 65 years, $p=0.05$) and received more preoperative cycles (median 6 vs. 4, $p=0.003$) compared to those without delays. Patients with delays from neoadjuvant chemotherapy to interval debulking delays also had longer time from pathological diagnosis to preoperative chemotherapy (median 22 vs. 17 days, $p=0.014$) and longer time from interval debulking to first post-operative chemotherapy (median 37 vs. 30 days, $p=0.01$) compared to those without delays. There were no differences in other clinical variables including stage, histology, Charlson score, or rates of optimal debulking and complete gross resection (Table 1).

For the 34 women with delays from neoadjuvant chemotherapy to interval debulking, the most common reasons for delays were logistical 13 (38%), primarily due to delays in scheduling. Nine patients (26%) were delayed due to a prolonged period required for pre-surgical clearance. Four patients (12%) were delayed due to medical comorbidity or acute hospitalizations, and 1 patient (3%) was delayed due to persistent anemia/neutropenia. Three patients (9%) were delayed because they initially deferred surgery. One patient (3%) was delayed because her case required discussion at a multidisciplinary treatment planning conference. In 3 patients (9%) surgery was aborted due to extent of disease, which was felt to be unresectable after assessment in the operating room (Table S1).

Progression-free Survival Analysis

Among the 159 women, there were 113 events of progression (108 clinical recurrences and 5 deaths without recurrence). The median follow-up time in those without progression was 12.3 months (range; 1.6–32.9). On univariate analysis, delays from neoadjuvant chemotherapy to interval debulking were not associated with worse progression-free survival

(HR 1.55 95% CI 0.97–2.47, $p=0.062$). In those with delays from neoadjuvant chemotherapy to interval debulking, progression-free survival was 10.0 months (95% CI 6.4–10.8) vs. 11.5 months (95% CI 0.1–14.5) in those without delays. Presence of *BRCA* mutations (HR 0.61 95% CI 0.37–0.98, $p=0.038$), optimal debulking (HR 0.48 95% CI 0.29–0.78, $p=0.003$) and complete gross resection (HR 0.45 95% CI 0.31–0.66, $p<0.001$) were associated with improved progression-free survival, while increased number of preoperative cycles was associated with worse progression-free survival (HR 1.29 95% CI 1.1–1.51, $p=0.002$). Neither time from pathological diagnosis to preoperative chemotherapy nor time from interval debulking to first post-operative chemotherapy were associated with progression-free survival on univariate analysis (Table S2).

In multivariate models, delays from neoadjuvant chemotherapy to interval debulking were not associated with progression-free survival (HR 1.52 95% CI 0.94–2.45, $p=0.089$), even after adjustment for preoperative cycles and complete gross resection (Table 2 and Figure 2).

Overall Survival Analysis

Among the 159 women, there were 38 deaths observed. The median follow-up time in survivors was 18.0 months (range; 1.6–36.4). On univariate analysis, delays from neoadjuvant chemotherapy to interval debulking were associated with worse overall survival (HR 2.4 95% CI 1.2–4.77, $p=0.01$). In those with delays from neoadjuvant chemotherapy to interval debulking, median overall survival was 17.2 months (95% CI 14.4 - not estimable), and the 1-year overall survival rate was 86% (95% CI 66.3–94.6). In those without delays, median survival was not reached, and the 1-year overall survival rate was 89.7% (95% CI 82.5–94). Presence of *BRCA* mutations (HR 0.31 95% CI 0.09–1.02, $p=0.041$) and complete gross resection (HR 0.41 95% CI 0.22–0.77, $p=0.004$) were associated with improved overall survival, while stage IV disease (HR 2.53 95% CI 1.06–6.06, $p=0.031$) was associated with worse overall survival. Neither time from pathological diagnosis to preoperative chemotherapy nor time from interval debulking to first post-operative chemotherapy were associated with overall survival on univariate analysis (Table S3).

In multivariate models, delays from neoadjuvant chemotherapy to interval debulking were not associated with overall survival after adjustment for age, stage at diagnosis and complete gross resection (HR 1.66 95% CI 0.80–3.44, $p=0.174$). Only increasing age, stage IV disease, and failure to achieve complete gross resection were significantly associated with worse overall survival (Table 2 and Figure 3).

DISCUSSION

Delays from neoadjuvant chemotherapy to interval debulking occurred in 21% of women. Those with delays from neoadjuvant chemotherapy to interval debulking were older and received more preoperative cycles. Although delays from neoadjuvant chemotherapy to interval debulking were associated with worse overall survival on univariate analysis, this association disappeared after adjustment for age, stage and complete gross resection. In multivariate models, only a greater number of preoperative cycles and lack of complete gross resection were associated with worse progression-free survival. Time from

pathological diagnosis to preoperative chemotherapy and time from interval debulking to first post-operative chemotherapy were not associated with survival.

This is one of the first studies to examine multiple time periods during neoadjuvant therapy and reasons for delays. Most delays from neoadjuvant chemotherapy to interval debulking particularly those in the range of 43–60 days, were due to logistical constraints and prolonged pre-surgical clearance for complicated medical patients. This suggests the need for multidisciplinary collaboration and systems-level processes to facilitate a timely transition from chemotherapy to surgery. Delays lasting >60 days were primarily due to patient comorbidity, prolonged recovery from chemotherapy, and patient choices. Of note, the patient with the longest delay (139 days) had low-grade serous histology and initially refused surgery but then requested surgery. Although histologies other than high-grade serous were rare in this study (n=6), there may be differences in underlying biology that affect delays, which should be investigated in larger studies. Finally, in 3 patients (9%) surgery was aborted due to extent of disease, suggesting that there may be a group of patients experiencing significant delays from neoadjuvant chemotherapy to interval debulking who may not benefit from surgery.

Our study found that delays from neoadjuvant chemotherapy to interval debulking were associated with overall survival on univariate analysis, while other time periods (time from is to preoperative chemotherapy and time from interval debulking to first post-operative chemotherapy) were not predictive of survival. This contrasts with studies of primary debulking demonstrating the importance of time from interval debulking to first post-operative chemotherapy and the role of delays from surgery to postoperative chemotherapy on survival. This may be a function of receiving neoadjuvant therapy and should be investigated further. It is possible that time from interval debulking to first post-operative chemotherapy plays less of a role in these patients because of the systemic effects of neoadjuvant chemotherapy; the biological basis should be investigated further. Interestingly, being diagnosed at an outside institution was associated with longer time from diagnosis to initiation of chemotherapy, suggesting that logistical factors such as obtaining pathology slides and records may play a role.

Unlike other studies, we did not find an independent effect of delays from neoadjuvant chemotherapy to interval debulking on survival. Instead, we found that any influence on survival was accounted for by other clinical factors such as age, stage, preoperative cycles and complete gross section, which have been well described.^{16–18} Our group has long emphasized the importance of maximal cytoreduction leaving as little residual tumor as possible to improve survival.¹⁹

Our overall survival curve shows a sharp drop-off in patients with delays, suggesting aggressive underlying disease in the 12 women who experienced delays from neoadjuvant chemotherapy to interval debulking and deaths. Eleven of these 12 women had stage IV disease, and all had high-grade serous histology. Nine of the 12 were platinum resistant, and 2 of the platinum-sensitive patients progressed between 6–7 months from the time of their last platinum treatment.

The strengths of our study include its utilization of a prospective, comprehensive Ovarian Database to identify patients, evaluation of multiple time periods during neoadjuvant therapy, and inclusion of multiple clinical variables. Limitations include the small sample size and limited follow-up. As the prospective ovarian database grows with time, such a study could be repeated with a larger sample size and longer follow-up to better explore these relationships. In addition, utilization of neoadjuvant therapy may not be based solely on clinical factors such as stage and comorbidity but may equally depend on non-clinical factors such as race, income, geography and insurance,²⁰ which should be investigated further.

Our study also identified an increasing number of preoperative cycles as a predictor of worse survival. A meta-analysis of 835 patients undergoing neoadjuvant therapy for ovarian cancer found that each incremental increase in preoperative cycles was associated with a median decrease in survival of 4.1 months.²¹ Bogani et al. found that increasing preoperative cycle number, 4 vs. 3, may adversely affect survival. This should also be investigated further in future studies.

In summary, delays from neoadjuvant chemotherapy to interval debulking occur in approximately 1 in 5 women undergoing neoadjuvant therapy for newly diagnosed ovarian cancer. These women are usually older and receive more preoperative cycles. After considering other clinical variables such as age, stage and surgical outcomes, we found that delays from from neoadjuvant chemotherapy to interval debulking do not independently affect survival. This emphasizes the importance of maximizing cytoreduction to improve survival

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Iasonos reports personal fees from Mylan, outside the submitted work.

Dr. Chi reports personal fees from Bovie Medical Co. (medical advisory board and stock options), Verthermia Inc. (medical advisory board and stock options), C Surgeries (shareholder), and Intuitive Surgical Inc (stock ownership), outside the submitted work.

Dr. O’Cearbhaill reports personal fees from Clovis (medical advisory board) and Tesaro (medical advisory board), outside the submitted work.

Dr. Konner reports personal fees from Clovis (guest speaker), AstraZeneca (medical advisory board), and Immunogen (medical advisory board), outside the submitted work.

Dr. Aghajanian reports personal fees from Tesaro (medical advisory board), Immunogen (medical advisory board), Mateon Therapeutics (steering committee) and Cerulean Pharma (medical advisory board), grants and personal

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Time Intervals in Neoadjuvant Chemotherapy (NACT)

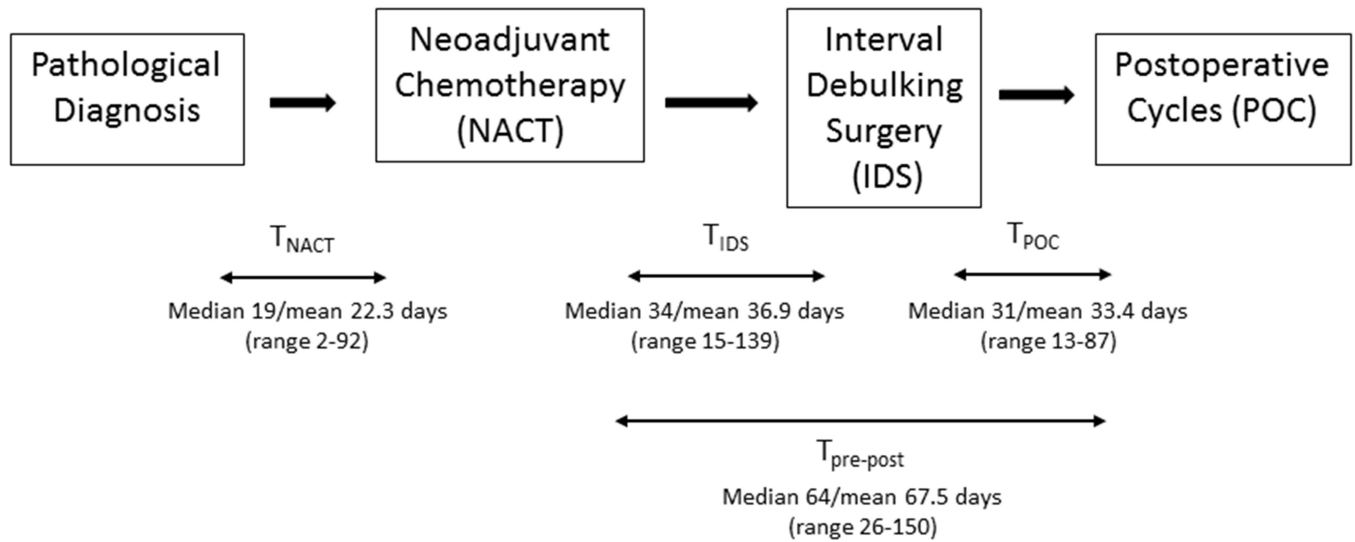


Figure 1.

Time Intervals in Neoadjuvant Chemotherapy (NACT) Time from pathological diagnosis to preoperative chemotherapy cycles was defined as T_{NACT} . Time from last preoperative carboplatin to interval debulking surgery was defined as T_{IDS} . Time from interval debulking to postoperative chemotherapy was defined as T_{POC} . Time from last preoperative carboplatin to first postoperative chemotherapy was defined as $T_{Pre-Post}$.



Figure 2: Progression-Free Survival (PFS) by T_{IDS} Delays T_{IDS} delays were not significantly associated with progression-free survival on univariate analysis.

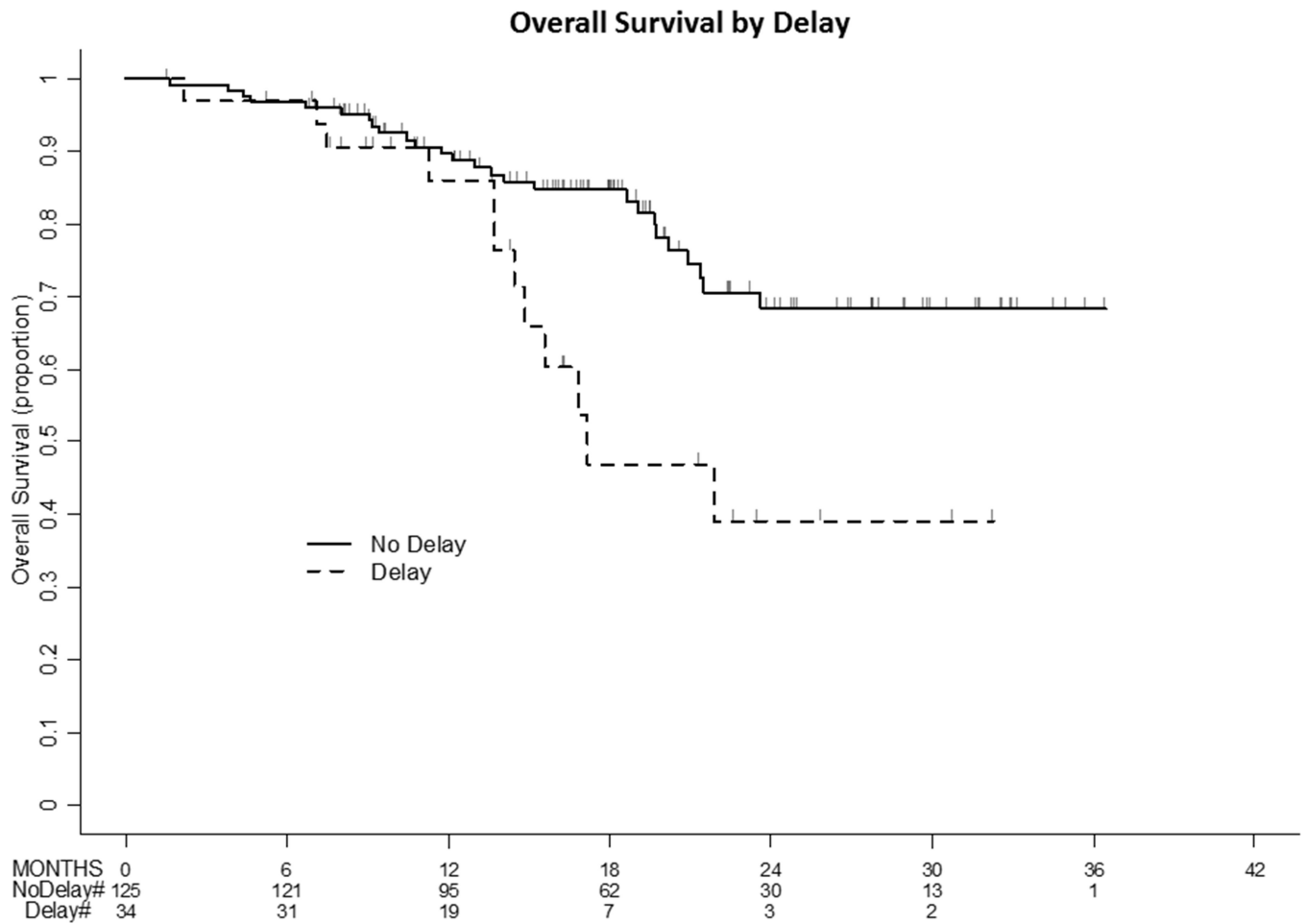


Figure 3: Overall Survival (OS) by T_{IDS} Delays Although T_{IDS} delays were significantly associated with overall survival on univariate analysis, this was attenuated after adjustment for age, stage and complete gross resection. T_{IDS} delays are not independently associated with overall survival.

Table 1:Patient characteristics, overall and by T_{IDS} delays

	All Patients N= 159	T _{IDS} Delay 34(21.4%)	No Delay 125(78.6%)	p-value*
Age				
Median(Mean)	66(65.8)	67.5(68.8)	65(64.9)	0.05
Range	43–87	44–86	43–87	
BRCA Mutations				
No mutation	101(63.5%)	24(70.6%)	77(61.6%)	0.67
BRCA mut/VUS	28(17.6%)	5(14.7%)	23(18.4%)	
missing	30(18.9%)	5(14.7%)	25(20%)	
Stage at Diagnosis				
III	50(31.4%)	7(20.6%)	43(34.4%)	0.148
IV	109(68.6%)	27(79.4%)	82(65.6%)	
Histology				
High grade serous	153(96.2%)	33(97.1%)	120(96%)	1
Other	6(3.8%)	1(2.9%)	5(4%)	
BMI (6 missing)				
Median(Mean)	25.5(27.5)	24.1(27.3)	25.9(27.6)	0.239
Range	15.4–60.1	18.4–46.8	15.4–60.1	
CA125 Cycle 1 (46 missing)				
Median(Mean)	1170(3203.3)	1043(3700.9)	1182.5(3061.9)	0.939
Range	4–38600	95–38600	4–29680	
CA125 Pre-surgery (80 missing)				
Median(Mean)	42(163.1)	44.5(174.1)	41(132.9)	0.571
Range	1–1901	1–1901	4–749	
Charlson Score				
Median(Mean)	8(8.5)	9(8.8)	8(8.4)	0.102
Range	6–12	6–12	6–12	
Albumin (1 missing)				
Median(Mean)	3.8(3.7)	3.8(3.7)	3.8(3.7)	0.872
Range	2.3–4.9	2.3–4.8	2.3–4.9	
KPS (47 missing)				
Median(Mean)	80(80.6)	80(79.5)	80(80.9)	0.874
Range	50–100	50–90	50–100	
Reason for Neoadjuvant Chemotherapy				
Disease Extent	111(69.8%)	22(64.7%)	89(71.2%)	0.724

	All Patients N= 159	T _{IDS} Delay 34(21.4%)	No Delay 125(78.6%)	p-value*
Comorbidity				
Both	8(5%)	1(2.9%)	7(5.6%)	
Other	32(20.1%)	9(26.5%)	23(18.4%)	
	8(5%)	2(5.9%)	6(4.8%)	
Chemotherapy Regimen				
Weekly Paclitaxel/Carboplatin	121(76.1%)	25(73.5%)	96(76.8%)	0.658
Others	38(23.9%)	9(26.5%)	29(23.2%)	
Preoperative Cycles				
Median(Mean)	4(4.2)	6(4.9)	4(4)	0.003
Range	2–7	3–6	2–7	
Dose Reduction				
No	142(89.3%)	30(88.2%)	112(89.6%)	0.762
Yes	17(10.7%)	4(11.8%)	13(10.4%)	
T_{IDS} (days)				
Median(Mean)	34(36.9)	48(56.7)	32(31.4)	-
Range	15–139	43–139	15–42	
T_{NACT} (days)				
Median(Mean)	19(22.3)	22(28.8)	17(20.6)	0.014
Range	2–92	6–77	2–92	
T_{POC} (days)[†]				
Median(Mean)	31(33.4)	37(39.4)	30(32.2)	0.01
Range	13–87	15–84	13–87	
Complete Gross Resection				
No	53(33.3%)	11(32.4%)	42(33.6%)	1
Yes	106(66.7%)	23(67.6%)	83(66.4%)	
Optimal Debulking				
No	20(12.6%)	7(20.6%)	13(10.4%)	0.143
Yes	139(87.4%)	27(79.4%)	112(89.6%)	

* p value is obtained by using Fisher-exact test for categorical variables and Wilcoxon rank sum test for continuous variables

[†] Only for the patients who received postoperative chemotherapy

Table 2:

Multivariate Model of Progression-Free and Survival (PFS) and Overall Survival(OS)

Progression-free Survival				
Variable	HR	Lower 95%CI	Upper 95%CI	p-value
T_{IDS} Delay (Yes vs. No)	1.516	0.938	2.451	0.089
Preoperative Cycles (Continuous, increase by 1)	1.256	1.073	1.47	0.005
Complete Gross Resection: Yes vs. No	0.432	0.295	0.633	<0.001
Overall Survival				
Variable	HR	Lower 95%CI	Upper 95%CI	p-value
T_{IDS} Delay (Yes vs. No)	1.659	0.799	3.442	0.174
Age (Continuous, increase by 5 years)	1.185	1.006	1.396	0.043
Stage: IV vs. III	2.683	1.082	6.651	0.033
Complete Gross Resection: Yes vs. No	0.469	0.244	0.902	0.023