

Impact of delay in interval debulking surgery after neoadjuvant chemotherapy on survival in ovarian cancer

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Abstract

Objective: To determine the impact of delay between neoadjuvant chemotherapy and cytoreductive surgery on progression-free survival and overall survival in ovarian cancer cases.

Method: The retrospective study was conducted at the Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan, and comprised data from January 2019 to January 2022 of women diagnosed with stage III high-grade serous ovarian cancer who received neoadjuvant chemotherapy and underwent subsequent interval debulking surgery. The patients were divided into groups A and B based on time to surgery within 6 weeks and time to surgery more than 6 weeks, respectively. The endpoint was taken as progression-free survival and overall survival on follow-up. Data was analysed using SPSS 27.

Results: Of the 2,100 patients who underwent surgery for ovarian cancer, 118(5.6%) women with mean age 52.18±9.3 years (range: 28-73 years) were included; 53(45%) in group A and 65(55%) in group B. Overall recurrence rate in this cohort was 76(64.4%); 36 (67.9%) in group A and 40 (61.5%) in group B. The mean progression free-survival was 15±1.5 months in group A and 18±2 months in group B (p=0.854). The mean overall survival across the sample was 44±1.8 months, and intergroup difference was not significant. (p=0.336).

Conclusion: Delay in interval debulking surgery after neoadjuvant chemotherapy was not found to have a significant impact on progression-free survival and overall survival in ovarian cancer cases.

Key Words: Ovarian cancer, Neoadjuvant chemotherapy, Debulking.

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Introduction

Ovarian cancer is one of the leading causes of morbidity and mortality in gynaecological cancers worldwide. The clinical presentation of ovarian cancer includes a series of non-specific symptoms, such as abdominal distension, bloating and pelvic pain.¹

In the absence of alarming symptoms along with the background of lack of insight and relative hesitance in seeking medical attention that is rampant in Pakistan, many people present to hospitals with advanced stages of the disease.² Advanced stage ovarian cancer treatment includes a combination of chemotherapy and surgical debulking of the disease. The introduction of neoadjuvant chemotherapy (NACT) for the reduction of

tumour load followed by interval debulking surgery has shown to have proven survival benefit.³ There is an arbitrary time period defined as 4-6 weeks that is currently considered appropriate when surgery should be done after the last chemotherapy dose. The appropriateness of the time interval between NACT and surgery requires a balance between allowing sufficient time for recovery from chemotherapy side effects, making sure the patients are fit for surgery preoperatively in relation to the risk of the disease progressing; rendering it not amenable to optimal surgical debulking.⁴ This is the current institutional practice for ovarian cancer interval debulking surgeries at the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC) in Pakistan. There are, however, delays noted that extend this interval to >6 weeks, which have been observed locally and are also very well recognised worldwide.⁵ The reasons for delay range from logistical issues, patient factors, need for discussion in multidisciplinary team meeting, etc. There is a need to explore if a delay of >6 weeks between NACT and interval debulking surgery has an impact on progression-free survival (PFS) and overall survival (OS) because a significant impact on survival will warrant minimising delays and better service provision, while minimal or no impact will help allay patient anxiety around the delay.⁶ A delay of >6 weeks after the last preoperative chemotherapy is usually considered late.⁷

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The current study was planned to determine the impact of delay between NACT and cytoreductive surgery on PFS and OS in ovarian cancer cases.

Materials and Methods

The retrospective study was conducted at the Department of Surgical Oncology, SKMCH&RC, Lahore, Pakistan, and comprised data from January 2019 to January 2022. Data was retrieved using total population sampling / universal sampling technique after approval from the institutional ethics review board.

Data related to women diagnosed with stage III high-grade serous ovarian cancer who received NACT and underwent subsequent interval debulking surgery. Stage III/IV disease at the time of diagnosis (histopathological or cytological) with imaging supporting an adnexal pathology had been discussed at a multidisciplinary team meeting which recommended NACT as the first treatment. The histopathological diagnosis post-surgery had not been relied upon for these patients; the rationale being that chemotherapy would have already downstaged the disease at that point.

All patients who had a poor Eastern Cooperative Oncology Group (ECOG)⁸ performance status at presentation (ECOG >3), incomplete follow-up or still under treatment, stage I/II disease, histology other than high-grade serous cancer, like mucinous, borderlines serous/mucinous, germ cell tumours, sex cord stromal, small cell, clear cell, and endometrioid ovarian cancers, morbid obesity (body mass index [BMI] >40kg/m²), incomplete chemotherapy data, referral to outside facility for chemotherapy, and patients who contracted coronavirus disease-2019 (COVID-19) during treatment were excluded. This was done to minimise the bias caused by concurrent comorbidities, different pathophysiology of the various histological types of ovarian cancers and lack of PFS and OS data. Also excluded was data related to patients who had been found to have unresectable disease after NACT and received further chemotherapy.

OS was determined by evaluating the number of deaths amongst the study group during follow-up. The time interval from completion of treatment to the time of death or last follow-up was noted.

Neoadjuvant time intervals were defined as within 6 weeks and more than 6 weeks, dividing the data into two cohorts. The time

interval was calculated in weeks and days from the date of the last cycle of chemotherapy to the date of the debulking surgery. The patients were divided into groups A and B based on time to surgery (TTS) within 6 weeks and TTS more than 6 weeks, respectively.

All patients who underwent interval debulking surgery required adjuvant chemotherapy with carboplatin and paclitaxel, some requiring maintenance therapy with bevacizumab. Upon the completion of treatment, they were put on surveillance with regular tumour marker cancer antigen-125 (CA-125) and imaging analysis. Disease recurrence was investigated upon biochemical elevation in tumour markers, subjective complaints of the patients or radiological evidence of recurrence.

Data was analysed using SPSS 27. Qualitative data was described as frequencies and percentages, while quantitative variables were expressed as mean \pm standard deviation. The Kaplan-Meier method was used to estimate median PFS and OS of all the patients as well as of the two groups. $P < 0.05$ was considered statistically significant.

Results

Of the 2,100 patients who underwent surgery for ovarian cancer, 118 (5.6%) women with mean age 52.18 ± 9.3 years (range: 28-73 years) were included; 53 (45%) in group A and 65 (55%) in group B. The mean BMI was 26.7 ± 5.4 kg/m² (range: 12-39 kg/m²). The mean CA-125 level was 2402.7 ± 3131.6 (range: 44.7-16382). Overall recurrence rate in this cohort was 76 (64.4%); 36 (67.9%) in group A and 40 (61.5%) in group B.

Mean PFS for the whole sample was noted (Figure 1). It was 15 ± 1.5 months in group A and 18 ± 2 months in group B.

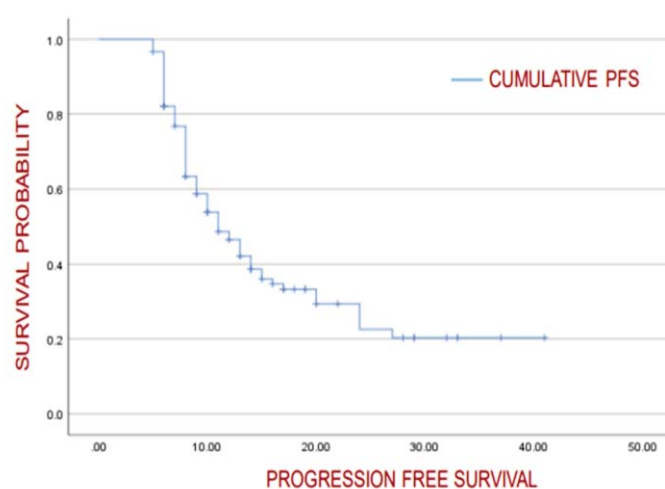


Figure-1: Progression-free survival (PFS).



Figure-2: Intergroup comparison of progression-free survival (PFS).

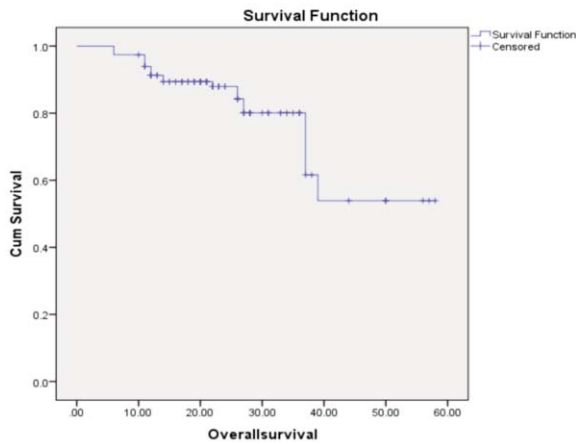


Figure-3: Overall survival (OS).

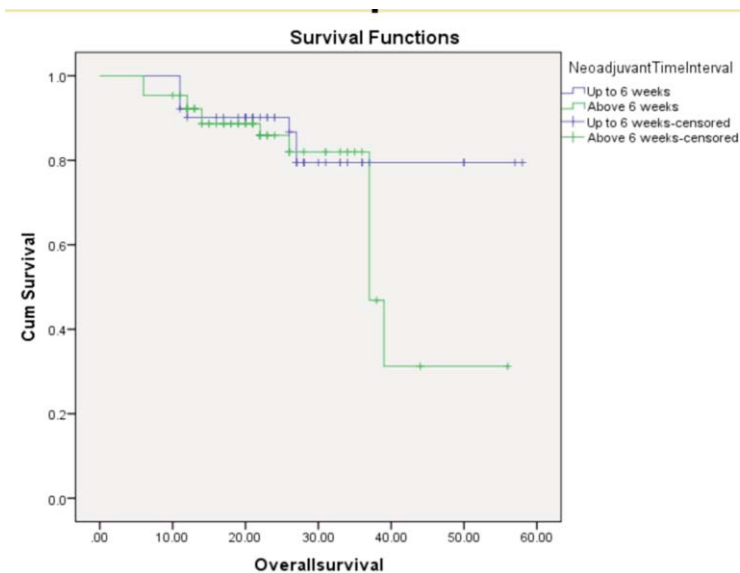


Figure-4: Intergroup comparison of overall survival (OS).

B ($p=0.854$) (Figure 2). The mean OS across the sample was 44 ± 1.8 months (Figure 3); 50 ± 1.6 months in group A and 39 ± 1.9 months in group B ($p=0.336$) (Figure 4).

Overall, 2(1.7%) patients were lost to follow-up and their data was excluded from OS analysis. Of the remaining 116(98.3%) patients, 21(18.1%) died during follow-up; 8(38%) in group A and 13(62%) in group B.

Discussion

The combination of NACT and interval debulking surgery is useful for treating advanced ovarian cancer.⁹ However, since this approach requires a multidisciplinary collaboration, delay between chemotherapy and surgery has been recognised, and the benefit of NACT is feared to be reduced if debulking surgery is not attempted within an appropriate timeframe.¹⁰ The reasons that amount to this delay are usually multifactorial. Other than service provision paucity in some cases, many patient factors are also responsible for this delay as recovering from chemotherapy and its side-effects is usually required for the patients to be fit to undergo surgical intervention.

In 2018, Chen M et al. conducted a retrospective study to determine the appropriate time interval between NACT and interval debulking surgery. TTS for advanced stage III/IV ovarian, tubal and peritoneal cancers was divided into two groups TTS >4 weeks and TTS ≤ 4 weeks. A longer PFS was noted in the group that received surgery <4 weeks (26 months, $p=0.04$) compared to those who received surgery after 4 weeks (14 months). OS was not found to be different in the two groups.¹¹

A follow-up study in 2020 assessed delays from NACT to interval debulking surgery and survival in ovarian cancer cases. Delay was defined as time interval >6 weeks. The delay was associated with a worse OS outcome. However, when adjusted for variables, such as age, stage and complete gross resection, survival was not significantly shortened. PFS was also not found to be affected by interval between NACT and surgery, and the only significant variables affecting PFS were increase in the number of preoperative chemotherapy cycles and suboptimal cytoreductive surgery.¹²

In 2023, a study tried to determine optimal time interval between neoadjuvant platinum-based chemotherapy and interval debulking surgery in high-grade serous ovarian cancer cases. Median PFS was 15.7 months and median OS was 44.7 months. An interval of ≥ 4 weeks significantly shortened PFS and OS ($p=0.004$ and $p=0.002$, respectively). Median PFS was 26.6 months for patients undergoing interval debulking surgery at <4 weeks.¹³

Conclusion

The time lapse between NACT and interval debulking surgery had no significant impact on PFS and OS in ovarian cancer cases.

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Authors Contribution:

KAK: Study design and concept, data acquisition, analysis and interpretation, drafting.

MH: Data acquisition, analysis and interpretation.

ASU, AWA & AAS: Supervision, final approval.

MAS: Data acquisition.

All authors agreement to be accountable for all aspects of the study.