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Original Research Article

Effect of time interval from completion of neoadjuvant chemotherapy to starting of adjuvant chemotherapy after interval debulking surgery on survival of patients with advanced ovarian cancer

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ABSTRACT

Background: To find the effect of time interval between completion of neo adjuvant chemotherapy to the starting of adjuvant chemotherapy on the RFS and OS of patients with advanced ovarian cancers.
Methods: It is a retrospective study of 170 patients with histopathological proven epithelial ovarian cancers who received full treatment (NACT+IDS+POAC) at Gujarat cancer Research Institute, Ahmedabad between 2010- 2016. They were assessed and followed up for maximum 5 year. The time interval was defined as period from the completion of NACT including Interval de-bulking surgery to initiation of chemotherapy.
Results: Out of 170 patients, 86 patients (50.5%) received adjuvant chemotherapy within 44 days after neoadjuvant chemotherapy while 84 patients (49.4%) received it after 44 days. There was no significant difference in patient characteristics between these two groups. The shorter and longer TI was having recurrence in 40 (53.48%) and47 (55.55%) patients respectively. Whereas overall survival was 67.44% and 47.61% respectively.
Conclusions: Our analysis showed that patients with longer time interval >44 days had poorer recurrence free survival and overall survival in comparison to lesser TI group.

Keywords: Neoadjuvant therapy, Interval de bulking surgery, Postoperative adjuvant therapy, Overall survival, Recurrence free survival, Time interval, Time to chemotherapy, Time to surgery

INTRODUCTION

Worldwide ovarian cancer affects over 2,00,000 women per year. Epithelial ovarian cancer has highest mortality rate of all gynecological malignancy, as more than two-third of cases are diagnosed in late stage.[1]

Due to advancement in treatment modalities the death rates have been falling on average 1.6% per year over 10 years.[2]

Historically, primary tumour reductive surgery was attempted followed by postoperative chemotherapy in most patients diagnosed with advanced ovarian cancer. In phase of evolution, neoadjuvant chemotherapy followed by interval debulking surgery is an alternative approach for patients with advanced-stage ovarian cancer.[3] As shown in multiple studies like EORTC and CHORUS that both modalities of treatment have equal outcome.[4-7]

However, there are some studies who showed the unanswered questions still need to be investigated and discussed, such as the optimal timing for IDS and perioperative chemotherapy. The aim of our study is to find out the effect and importance of time interval between end of NACT and initiation of adjuvant chemotherapy on OS and RFS. There are some who importance of time

interval in reference to adjuvant therapy after upfront surgery. As per these studies longer the interval is associated with poor prognosis.

METHODS

In this retrospective study we analysed the clinical data of 200 patients belonging to FIGO stage III- IV of epithelial ovarian cancer who underwent full treatment (NACT+IDS+ADJ.CT) at GCRI Ahmedabad between 2010 to 2016.

Inclusion criteria

Histopathological proven epithelial ovarian cancer or (if biopsy done outside, slide and blocks available for review). Advance ovarian cancer FIGO stage III- IV. Patient had received 3 cycles of neoadjuvant chemotherapy paclitaxel and carboplatin (P+C) followed by surgery and then 3 cycle of adjuvant chemotherapy. Had not received any other chemotherapy or PARPi as maintenance therapy. Patients with regular follow up for 5 years or till death.

Exclusion criteria

We excluded those patients, who had taken any of the treatment (NACT, IDS, ADJ.CT) outside our institute (n=17). Whose complete medical records were not available (n=6). Did not have regular follow-up records (n=7). Ultimately, the final number of patients for study was 170.

As per our institute protocol, patients with any one of the following criteria were referred for NACT 1) pulmonary and/or hepatic parenchymal metastases were observed on imaging studies before surgery, 2) optimal cyto reduction was not achievable due to a high tumor burden. 3) Moderate to severe ascites and CA-125 >500.

Before neo adjuvant chemotherapy, all the patients had histological diagnosis either by biopsy or cytology from ascites or pleural effusion with IHC report. The selected regime for NACT and Adjuvant chemotherapy was paclitaxel (280) and carboplatin (AUC 5-6).

Interval debulking surgery (IDS) were done by laparotomy. Standard surgical procedures included a thorough exploration of the abdomen and pelvis followed by hysterectomy, bilateral oophorectomy and omentectomy. Cytoreductive surgery included bowel resection; diaphragm or other peritoneal surface stripping; splenectomy; liver resection. Postoperative complications were graded according to the Calvin Dindo classification; Operative mortality was defined as death occurring within 30 days after surgery (grade 5).

In our study time interval (TI) was explained as the duration between the completion of NACT and the starting of POAC. The time to surgery (TS) was defined as the time (in days) from the end of NAC to IDS, while the time to chemotherapy (TC) was defined as the time from IDS to the initiation of POAC.

End point of this study was to find out the effect of time interval on overall survival (OS) and recurrence free survival (RFS). OS was defined as interval between the date of diagnosis and date of death. Whereas RFS was defined as time interval between date of diagnosis and appearance of first recurrence. The present study was reviewed and approved by our Institutional ethic committee.

Our institutional protocol is to follow-up patients every 3 months for the first 2 years after treatment and every 4 months thereafter. Recurrence was defined as the date of appearance of radiologically-detected disease during a follow-up examination. A rise of CA-125 without clinical signs of relapse was not counted as progression but generally arise suspicion and trigger further radiological examinations.

We routinely performed CA-125 and imaging studies for surveillance.

We collected and analysed all the data like Age, body mass index, pre-treatment serum cancer antigen-125 (CA-125) levels, FIGO stage, American Society of Anesthesiologists (ASA) score, histology, performance of radical surgery, chemotherapy regimens, residual disease after IDS, total chemotherapy cycles, date of surgery, date of starting and ending NAC and POAC initiation, date of progression or recurrence, and last follow-up from the medical records. For the survival we had contacted relative on phone and asked in detail.

Statistical analysis

SPSS statistical software (version 20.0; IBM Corp., Armonk, NY) was used for the statistical analyses. Descriptive statistics were used for demographic data and are summarized as the median (range) or frequency (percentage). Differences in the patient characteristics were compared in relation to the time intervals using the chi-square. PFS and OS were analysed with the Kaplan-Meier method and log-rank. Test P value 0.05 was considered statistically significant.

RESULTS

Out of 200 patients, 170 patients were included in our study after applying inclusion and exclusion criteria. The median age in our study group was 52 years. Majority of the patients had FIGO stage III c (n=70, 41.17%) and stage IV disease (n=66, 38.81%). Serous histology was present in 159 (93.52%) patients, mucinous histology in 6 (3.52%) patients and other histology was present in 5 (2.94%) patients. The pre-treatment, median baseline CA-125 was 1386. Before IDS, median CA-125 was 70 and was

normal in 78 patients. All these patients with normal CA-125 was optimally cytoreduced.

Patients are divided in two group, shorter TI (<44days) and longer TI (>44days) to evaluate the importance of time interval in our study. These group included 86 (50.5%) and 84 (49.41%) patients respectively.

Patients' characteristic such as BMI, ASA score, baseline CA-125, histology, CA-125 before IDS, FIGO stage, surgery extent, residual disease, complication rate and cycle of chemotherapy between 2 groups were almost similar and taken in account for analysis are shown in table 1 and 2.

After 5 years follow-up, 87 (51.17%) patients had recurrence and 62 (36.47%) died due to disease. Among the 87 patients of the recurrence, 40 (46.51%) were in shorter TI and 47 (55.5%) were in longer time interval. All patients with recurrence were biopsy or cytology proven.

Out of 62 patients who died 28 (32.55%) died in shorter interval and 34 (40.47%) in longer interval group. So, as per our study both recurrence and death rate were higher among patients in longer time interval. In 84 patients in longer TI group 54 patients had delayed time of surgery whereas 30 patients had delayed adjuvant chemotherapy.

Kaplan-Meier curve for OS and RFS are shown in Figure 1 and 2. Patients in shorter TI had better RFS (P=0.057) and OS (P=0.0469) in comparison to longer TI group. So our study confirmed that patients with longer TI between NACT and POAC were found to have more risk of recurrence, death and poor OS and RFS.

Table 1: Patients and clinical features.

Interval in days	<44 days	>44 days		
	N=86	N=84	Total	P- value
Median age	52 (32-74)	51 (31-74)	52	0.0440
Median baseline CA-125	1386 (172-11160)	1321 (52-17574)	1386 (52-17574)	0.006
Median preop CA-125	67.5 (6-1084)	82 (8-1653)	70 (6-1653)	0.005

Table 2: Interval days.

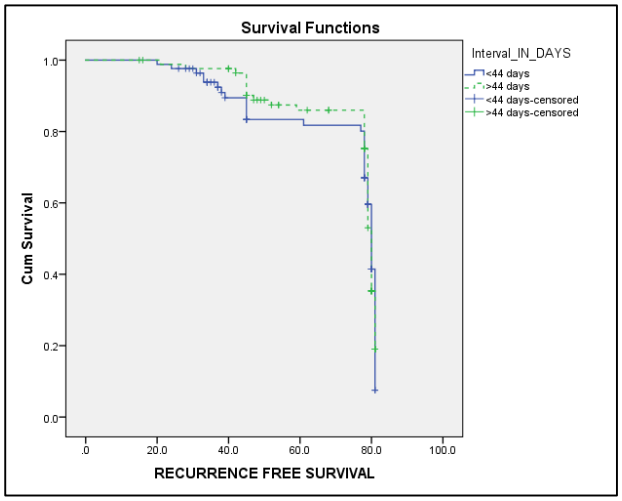
Interval in days		Shorter TI<44 days	Longer TI>44 days			
		N=86 (50.58%)	N=84 (49.41%)	Total	%	P- value
Stage	Stage IIIA	1 (1.16%)	3 (3.57%)	4	2.35	0.010
	Stage IIIB	23 (26.74%)	7 (8.33%)	30	17.64	
	Stage IIIC	29 (33.72%)	41 (48.80%)	70	41.17	
	Stage IVA	24 (27.90%)	23 (27.38%)	47	27.64	
	Stage IVB	9 (10.4%)	10 (11.90%)	19	11.17	
HPE	Serous	82 (95.34%)	77 (91.66%)	159	93.52	0.926
	Mucinous	2 (2.32%)	4 (4.76%)	6	3.52	
	Others	02 (2.32%)	03 (3.57%)	5	2.94	
Radical SX	No	62 (74.69%)	65 (77.38%)	127	74.70	0.464
	Yes	24 (27.90%)	19 (22.61%)	43	25.29	
Residual DS	No	77 (89.53%)	47 (55.95%)	124	72.94	0.001
	Yes	9 (10.46%)	37 (44.04%)	46	27.05	

Table 3: Recurrence free survival.

Interval in days	Number of recurrences	No recurrence
<44 days, N=86	40 (46.51%)	46 (53.48%)
>44 days, N=84	47 (55.95%)	37 (44.04%)
Overall	87 (51.17%)	83 (48.82%)

Table 4: Overall survival.

Interval in days	Number of deaths	Number of alive
<44 days, N=86	28 (32.55%)	58 (67.44%)
>44 days, N=84	34 (40.47%)	40 (47.61%)
Overall	62 (36.47%)	98 (57.64%)



p-value 0.0570

Figure 1: Recurrence free survival during follow period of 5 years.

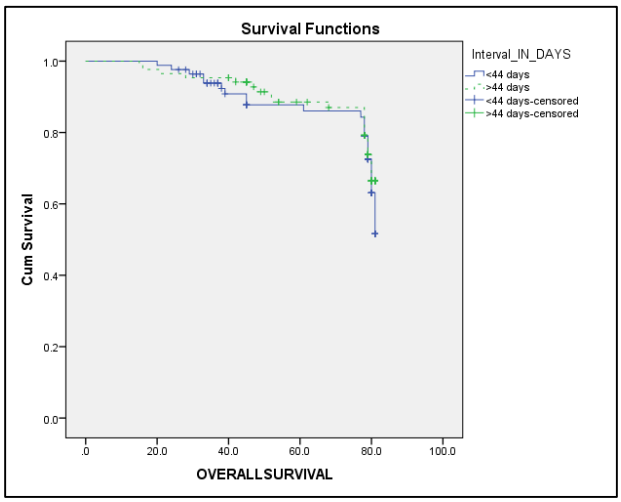


Figure 2: Overall survival during follow up of 5 years.

Table 5: Overall comparisons.

Overall comparisons (overall survival)			
	Chi-Square	**df**	**Sig.**
Log rank (mantel-Cox)	0.523	1	0.0469

p-value 0.0469

DISCUSSION

Recent guidelines recommend that NACT is be a better option for patients who are not fit for primary surgery because they have an unacceptable surgical risk or unresectable disease, and in recent years, the use of NACT has gradually increased.[8]

In this study we analysed the question whether timing between NACT and ADJ CT has any effect on overall survival of the patients. Despite of commonly accepted use of this sequential treatment, there is no guideline on the optimal interval between NACT, debulking surgery and the start of adjuvant chemotherapy. While general consensus supports avoiding unnecessary delays, there are very few studies on the ideal time interval and its impact on survival. It is expected that commencement of adjuvant chemotherapy should be as soon as possible, to prevent early tumour growth.

In our study, patients were divided in longer TI (>44days) and shorter TI (<44 days), to find the effect of time interval on survival and recurrence. Recurrence and death rate in shorter time interval was 46.51% and 32.55% respectively. While recurrence and death rate were more in longer TI that is 55.95% and 40.47% respectively. These results are similar to studies done by Timmermans et al and Tewari et al. These two studies have shown worse survival when chemotherapy was started after 37 and 25 days, respectively.[9,10] Seagle et al reported the most important positive result. Data was collected from the National Cancer Data Base and analysed 15,752 patients belonging to American population with ovarian cancer, and concluded that a delay in chemotherapy >35 days was associated with a 7% increased risk of death. It provides information about possible modifiable characteristics and can help to minimize the time interval between surgery and adjuvant chemotherapy.[11]

Importance of time interval had been studied in other cancers also. Colorectal and Breast cancer showed that delayed starting of adjuvant chemotherapy impairs overall survival.[12-15] There are some studies failed to show an association between the 'Time interval' (TTC) and overall survival.[16] There are multiple studies on effect of time interval between NACT- IDS, and IDS - adjuvant CT but to our knowledge, there are few studies demonstrating the effect of entire time interval (NACT - ADJ.CT) on survival and recurrence.

There are various reasons for delay in surgery after NACT. The most common reason encountered was chemotherapy related toxicity. The accepted practice is to perform IDS, when neutropenia has resolved, which normally requires 3- to 4-week time interval.[17,18] Hence most IDS are performed after this time interval. Some of the patients have delayed in recovery of haematological parameters. These may be due to poor nutritional status and response to the chemotherapy. Nutritional status can be improved by proper supplement and advice regarding proper diet. Other reasons for delay in IDS are comorbidities like HTN, DM, educational, social and financial issues and hospital constrain. As we have seen in our study the social issues play an important role for delay in surgery. As many patients are poor and illiterate, their compliance is very poor for antihypertensive and antidiabetic drugs. Lee YJ et al pointed on new problem which delay in surgery that is planning of surgery by multidisciplinary team.[19]

Multiple factors, like tumour and surgery-related factors may cause delay in adjuvant chemotherapy administration,

such as age comorbidity, extensive disease, infection and the extent of surgery.[20] In this study we come to know about factors that are related to a prolonged TTC. As reported in previous studies, longer hospital stays and postoperative complications were the strongest factors for delayed initiation of chemotherapy.[21] A complicated postoperative often leads to prolonged hospitalization due to additional medical interventions, and result in delayed chemotherapy administration. Patients with extensive surgery were more prone to delay in starting of adjuvant chemotherapy, probably they need more time recover from postoperative morbidities. Other prognostic factors like age, stage, residual stage, CA-125 are independent prognostic factor. In our study all factors except residual disease is comparable in both groups.

The right time interval between NACT and ADJ CT is an open point of discussion in routine practice It is general belief that chemotherapy should be started as early as possible after surgery, especially when surgery is of suboptimal type. Gunduz et al, stated that growth of tumour is more after resection, which may result from a conversion of non-cycling cells in G0 phase into proliferation.[22] Likewise, surgery has been shown modulate the function of the immune system for time being, antitumor effects of interleukin-2 and lymphokine-activated killer cells will be significantly reduced by the performance of a laparotomy.[23]

Chiang et al, found that the peak age of diagnosis of ovarian malignancy has changed from 60 years to 50 years from 1979 to 2008 in, this is also reflected in our study, where the mean age of diagnosis was 52.8 years.[24]

In spite of limitations of CA-125 in ovarian malignancy, this biomarker is widely used to evaluate therapeutic efficacy and monitor disease status. In our study all 78 patients with normal ca 125 had optimal cytoreduction, Pelissier A et al, concluded that a CA125 level less than 75 UI/ml after the 3rd NACT was an independent predictor factor for optimal IDS.[25]

Limitation of our study was that it was retrospective study, data derived from medical record and many patients were contacted on phone for survival and death. Our study evaluated all cause of mortality rather than disease specific.

Major strength of study is large number of patient (170) was analysed, and both the group had almost equal number of patients. All had received 3 NACT(P+C), then IDS and 3 adjuvants (P+C).

CONCLUSION

In addition to known prognostic factor, such as stage, residual disease after surgery and pre-operative CA-125, the time interval between preoperative and postoperative chemotherapy was found to be an independent prognostic factor for RFS and OS. Our study also demonstrated significant correlation between survival and TI. Longer time interval between NACT- POAC is associated with poor outcome. Further studies are required to justified the result.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. NIH. Cancer Stat Facts, 2017. Available at: https://seer.cancer.gov/statfacts/. Accessed on 20 March 2023.
3. Morgan RJ, Alvarez RD, Armstrong DK, Burger RA, Castells M, Chen CH, et al. Ovarian cancer, version 3.2012. J Natl Compr Cancer Netw. 2012;10:1339-49.
4. Vergote I, du Bois A, Amant F, Heitz F, Leunen K, Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: on what do we agree and disagree? Gynecol Oncol. 2013;128(1):6-11.
5. Nishio S, Ushijima K. Clinical significance of primary debulking surgery and neoadjuvant chemotherapy-interval debulking surgery in advanced ovarian cancer. Jpn J Clin Oncol. 2020;50(4):379-86.
6. Lv X, Cui S, Zhang X, Ren C. Efficacy and safety of neoadjuvant chemotherapy versus primary debulking surgery in patients with ovarian cancer: a meta-analysis. J Gynecol Oncol. 2020;31(2):e12.
7. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cance. N Engl J Med. 2010;363:943-5.
8. National comprehensive cancer network group. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer (Version 1.2018). Available at: NCCN.org. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed on 28th February 2018.
9. Timmermans M, van der Aa MA, Lalisang RI, Witteveen PO, Van de Vijver KK, Kruitwagen RF, et al. Interval between debulking surgery and adjuvant chemotherapy is associated with overall survival in patients with advanced ovarian cancer. Gynecol Oncol. 2018;150(3):446-50.
10. Tewari KS, Java JJ, Eskander RN, Monk BJ, Burger RA. Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study. Annals of Oncology. 2016;27(1):114-21.
11. Seagle BLL, Butler SK, Strohl AE, Nieves-Neira W, Shahabi S. Chemotherapy delay after primary

debulking surgery for ovarian cancer. Gynecol Oncol. 2017;144:260265.
12. Gagliato DdM, Gonzalez-Angulo AM, Lei X. Clinical impact of delaying initiation ofadjuvant chemotherapy in patients with breast cancer. J Clin Oncol. 2014;32:735-44.
13. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed initiation ofadjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2:322-9.
14. Des Guetz G, Nicolas P, Perret GY, Morere JF, Uzzan B. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer. 2010;1049-55.
15. Czaykowski PM, Gill S, Kennecke HF, Gordon VL, Turner D. Adjuvant chemotherapy for stage III colon cancer: does timing matter? Dis Colon Rectum. 2011;54:1082-9.
16. Feng Z, Wen H, Bi R. Prognostic impact of the time interval from primary surgery to intravenous chemotherapy in high grade serous ovarian cancer. Gynecol Oncol. 2016;141:466-70.
17. National comprehensive cancer network group. NCCN Clinical Practice Guidelines in Oncology. Myeloid growth factors (Version 1.2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.p df. Accessed on 2nd March 2018.
18. National comprehensive cancer network group. NCCN Clinical Practice Guidelines in Oncology. Cancer- and chemotherapy-induced anemia (Version 2.2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/anemia. pdf. Accessed on 21st November 2017.
19. Lee YJ, Chung YS, Lee JY, Nam EJ, Kim SW, Kim S, et al. Impact of the time interval from completion of neoadjuvant chemotherapy to initiation of postoperative adjuvant chemotherapy on the survival of patients with advanced ovarian cancer. Gynecol Oncol. 2018;148:62-7.
20. Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu YS, Lewin SN, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advance-stage ovarian cancer. Obstet Gynecol. 2012;120:871-81.
21. Hofstetter G, Concin N, Braicu I, Chekerov R, Sehouli I, Van Gorp CT, et al. The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma-analysis of patient data in the prospective OVCAD study. Gynecologic oncology. 2013;131(1):15-20.
22. Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetic so residual tumor. Cancer Res. 1979;39:3861-5.
23. Eggermont AM, Steller EP, Sugarbaker PH. Laparotomy enhances intraperitoneal tumor growth and abrogates the antitumor effects of interleukin-2 and lymphokine-activated killer cells. Surgery. 1987;102:71-8.
24. Chiang YC, Chen CA, Chiang CJ, Hsu TH, Lin MC, You SL, et al. Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan. J GynecolOncol. 2013;24:342-51.
25. Pelissier A, Bonneau C, Chéreau E, de La Motte Rouge T, Fourchotte V, Daraï E, et al. CA125 kinetic parameters predict optimal cytoreduction in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy. Gynecol Oncol. 2014;135(3):542-6.

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