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Neoadjuvant chemotherapy in advanced stage ovarian cancer

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Abstract
Background: Primary debulking surgery followed by platinum based chemotherapy was the standard therapy for advanced stage of ovarian cancer in the past. Primary debulking could be performed only in 30 to 60% of the patients with advanced ovarian cancer. In patients who had massive ascites, pleural effusion and large abdominal tumor, hence optimal primary debulking with gross residual disease less than 1 cm was difficult without Neoadjuvant chemotherapy (NACT). Hence present day guidelines suggest to give 3 – 4 cycles of Neoadjuvant chemotherapy to downstage the disease, which eventually helps the surgeon in obtaining optimal cytoreduction, which may transform into a prolonged disease free and overall survival.
Aim:
1. To study the radiological response of advanced ovarian cancer by RECIST (Response Evaluation Criteria In Solid Tumors) criteria using CT scan
2. To Evaluate the correlation of CA 125, pre NACT an post NACT.
3. To study the chemotherapy related changes in histopathological evaluation.

Materials and Methods: Patients diagnosed as Ca ovary stage III and IV underwent CT imaging and serum CA-125 estimation before and after NACT followed by interval debulking and adjuvant chemotherapy, Response to the Neoadjuvant chemotherapy will be analysed by RECIST criteria. During surgery intra op tumor size is observed and also presence of non- target lesions and documented. The specimen is then sent for histopathological examination to look for chemotherapy related changes.
Results: The study was conducted on 34 patients of whom 31 patients had partial response, 1 patient had stable disease and 2 patient had progressive disease after NACT. CA-125 was estimated in these patients prior and after NACT and was found to have reduction in the values which was statistically significant of p value of <0.0001, with mean and standard deviation of pre-operative and post-operative CA-125 being 1808.38± 2205.27 and 111.38± 181.84 respectively.
Conclusion: Our present study showed that NACT reduced the tumor burden and it allowed easier and complete surgical cytoreduction and also reduced surgical complications and treatment related deaths and morbidity. This study also showed that CA-125 is one of the best markers in epitheial ovarian cancer as it helps to assess the objective response to chemotherapy. It also helps to know the prognosis of the disease.

Keywords: Neoadjuvant chemotherapy- NACT, cancer antigen – CA-125

Introduction
Ovarian cancer is one of the leading causes of death among all gynecologic cancers. It is the 6th common cancer in women in developed countries. Most of them are diagnosed at advanced stage due to non-specific signs and symptoms hence resulting in poor outcome [1]. Primary debulking surgery followed by platinum based chemotherapy was the standard therapy for advanced stage of ovarian cancer. Several studies have shown that primary debulking surgery is associated high mortality and morbidity rates or will relapse and eventually die of progressive disease. In stage III and stage IV ovarian cancer primary debulking could be performed only in 30 to 60% of the patients. In advanced stage of ovarian cancer with massive ascites, pleural effusion and large abdominal tumor, primary debulking was difficult without NACT [1].
In bulky ovarian tumor, NACT has been found to be the best initial management before surgery, keeping in the view the main goal of peroforming optimal reduction. In a selected group of patients primary chemotherapy was found to have less complications and better quality of life and it also improved the prognosis in patients who have completed the course of NACT [2]
In this study, we aim to study the response of advanced stage ovarian cancer to NACT by RECIST [3] (Response evaluation criteria in solid tumors) criteria according to NCCN Guidelines Version 2.2014 [3] and to study the correlation of CA-125 pre- NACT and post- NACT.

Methods

This descriptive study was conducted in the Department Obstetrics and Gynecology, K.S. Hegde Medical Academy, Deralakatte, which is a teaching institute in the state of Karnataka, India. This study was conducted between November 2015 and August 2017.All patients who diagnosed with ovarian cancer underwent thorough physical examination, radiological studies (CT imaging), and histopathological confirmation (peritoneal fluid cytology or CT/USG guided biopsy) prior to NACT.

Estimation of CA 125 of all the patients was done prior to NACT and prior to interval debulking. Platinum based NACT was administered as primary treatment. Carboplatin was given at a dose of AUC 6 which is approximately 75mg/m^2, and Taxane 300mg/m^2. Chemotherapy was repeated every 3 weeks. Response to the NACT was analyzed on abdominal CT scan using RECIST criteria.

Surgery was performed in patients showing tumor response after median number of 3 cycles (range 3-6) of initial chemotherapy.

Interval debulking surgery was performed after 3 cycles (range from 3 to 6) of neoadjuvant chemotherapy. During surgery intra op tumor size was observed and also presence of non- target lesions were documented, the surgical specimen was sent for histopathological examination. Detailed histopathological evaluation was carried out for chemotherapy related changes. Five parameters were considered for assessment. That is, fibrosis, necrosis, residual tumor size, inflammation and psamomma bodies. Fibrosis is scored as mild 1+, moderate 2+, severe 3+. Necrosis is scored as absent (0), 1% - 50% (1+), and present >50% (2+), and >50% (3+). Residual tumor is scored as <5% (1+), 5-50% (2+), and >50% (3+). Inflammation is scored as mild (1+) and extensive (2+). Psamomma bodies is absent (0) and present (1+). After the surgery patient is followed up with adjuvant chemotherapy.

Serial CA-125 levels were also calculated during adjuvant chemotherapy follow-up.

Inclusion criteria

- All patients diagnosed with epithelial ovarian carcinoma stage FIGO III and IV
- All patients considered unresectable by the surgeon based on initial imaging evaluation.
- Patients with performance status of ECOG 1and 2**.**
- Patient who can give consent and above 18 yrs.

Exclusion criteria

- Patient with poor performance status ECOG 3 and 4
- Patient with non-epithelial ovarian malignancy like germ cell tumors and stromal tumors
- Patients less than 18 years and who cannot give informed consent
- Patient known allergic to chemotherapy drugs

Table 1:

Ecog [4] Performance Status	
Grade	**Ecog**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Recist response criteria [3]

1. Evaluation of target lesions

When more than one measurable lesion is present at baseline all lesions upto a maximum of five lesions total representative of all involved organ should be identified as Target lesions and will be recorded and measured at baseline

Table 2:

Complete Response (Cr)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm
Partial Response (Pr)	AT least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (Pd)	AT least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.in addition to relative increase of 20 % the sum must also demonstrate an absolute increase of at least 5mm. note: the appearance of one or more new lesions is also considered progression.
Stable Disease(Sd)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

2. Evaluation of non-target lesions

All other lesion (or sites of disease) including pathological lymph nodes should be identified as non – target lesions and should also be recorded at baseline.

Table 3:

Complete Response (Cr)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size < 10 mm short axis.
Non Cr/ Non Pd	Persistence of one or more non-target lesion (s) and/ or maintenance of tumor marker level above the normal limits
Progessive Disease (Pd)	Unequivocal progression of existing non-target lesions (one or more new lesions is also considered progression)

Statistical analysis: All data were entered in excel sheet and analysis of data was done using SPSS version 15 and Epi Info. The collected information was summarized using descriptive data as frequency, percentage, mean and standard deviation.

Chi –square test was used to analyze the response of NACT using RECIST criteria, to calculate on reduction of pre and post NACT CA-125 and also chemotherapy related changes. The p value of <0.05 was considered statistically significant

Results

Observation and Results

Total no of patients included in the study is 34.

Table 4: Age distribution in advanced stage disease

Range	29-70
Minimum	29
Maximum	70
Mean± Standard Deviation	51.32± 9.66

Above table shows the mean age group among the patients in advanced stage disease is 51.32 ± 9.66 years. Range of age 29-70 years.

Parity status of patients

This bar diagram shows that parity status of the patients was not related to the incidence of the disease. Para 2 and para 3 patients were having higher incidence of the disease compared to nulliparous where only 3 patients had the disease.

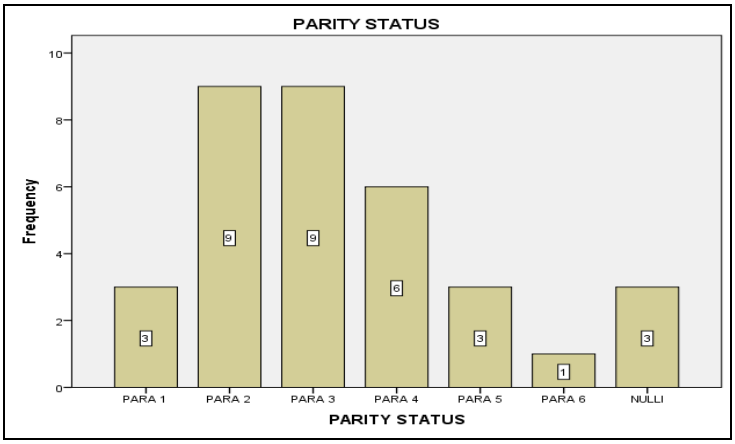


Fig 1: Parity status of patients radiological response to chemotherapy

This figure shows the Response of the patients after NACT therapy This diagram shows that 31 patients had complete response (91.17%) to Neoadjuvant chemotherapy following 3, 4 or 5 cycles.

In the group of patients who showed response to chemotherapy, sixteen patients had 3 cycles of NACT, 12 patients had 4 cycles of NACT and 3 patients had 5 cycles of NACT.

Two patients (5.88%) had progressive disease; one received 3 cycle and other 4 cycles respectively.

One patient (2.94%) had stable disease who received 6 cycles of NACT According to Pearson Chi- square there was significant (p=.0001) association between Response and number of NACT cycles. Patients who received 3 cycles of NACT showed more incidence of partial response than patient who received 6 cycles of NACT who had stable disease.

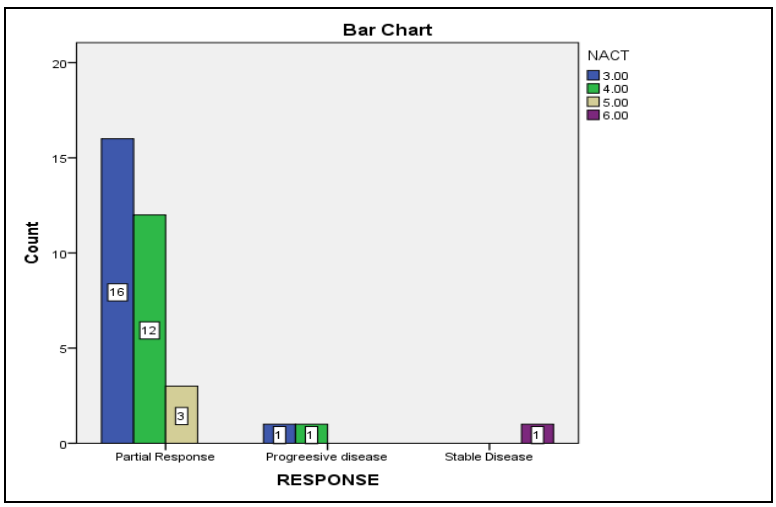


Fig 2: Radiological Response to Chemotherapy

There is significant reduction (P<0.0001) in CA-125 after the chemotherapy (NACT).

Table 5: CA-125 values before and after NACT.

Variables	Pre Nact Ca-125	Post Nact Ca-125
Value	9785 (maximum)	8 (minimum)
Standard Deviation	2205.27	181.84
Mean	1808.38	111.38

Table 6: Number of nact cycles received

No Of Cycles Received	Patients (N=34)
3	17 (50%)
4	13 (38.23%)
5	3 (8.82%)
6	1 (2.94%)

Table 7: Residual Tumor Size after Nact

Residual Tumor Size	Number (%) N=34
No residual tumor	26 (76.4%)
<1cm	5 (14.7%)
≥1cm	3 (8.82%)
Total	34

Out of the 34 patients who received NACT, 26 patients (74.4%) achieved no residual tumor after the interval debulking surgery 5 (14.7%) patients had less than 1cm residual tumor size, and 3 (8.82%) patients had more than or equal to 1cm.

Table 8: Histopathological evaluation for chemotherapy related changes

Histological Parameter		Grading (N = 34)	
Fibrosis	1+ 17(50%)	2+ 17(50%)	3+
Necrosis	0	1+ 23(67.64%)	2+ 11(32.35%)
Inflammation	1+ 10 (29.41%)	2+ 14(41.17%)	3+ 10(29.41%)
Residual Tumor	1+ 20(58.82%)	2+ 14(41.17%)	
Psammoma Bodies	0 34(100%)	1+ 0	

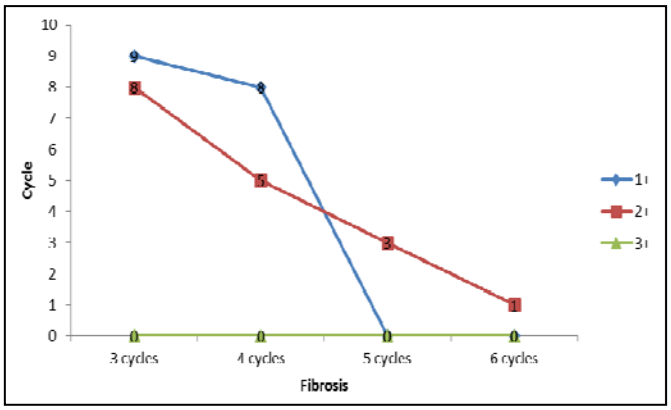
Table 9: Reduction Ca-125 Level and Residual Tumor Size

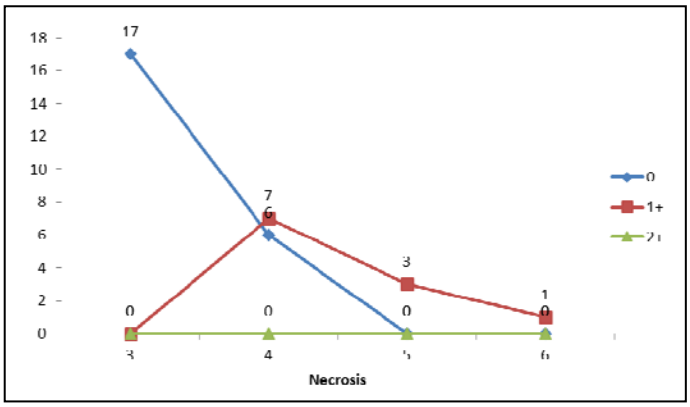
Residual tumor size (n=34)	Mean difference of reduction in CA-125
No residual tumor (26)	1950.88
<1cm (5)	437.22
≥1cm (3)	3193.66

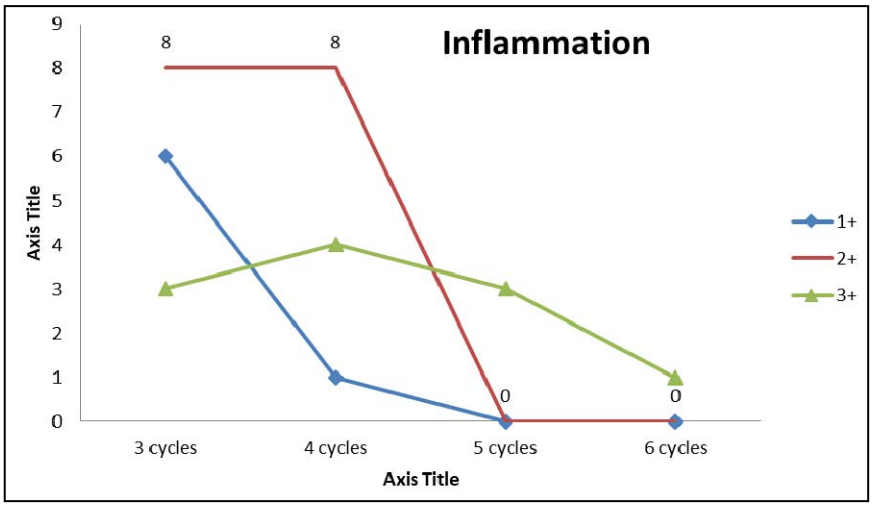
When mean difference of reduction in CA- 125 levels with residual tumor was studied it showed that, 26 patients with no residual tumor size had mean difference of reduction in ca-125 level by 1950.88, 5 patients with <1cm residual tumor was 437.22 and 3 patients with ≥ 1cm was 3193.66.

Table 10: Correlation number of cycles of chemotherapy with histopathological parameters

				Histopathology					
No of Nact Cycles	Fibrosis			Necrosis			Inflammation		
	1+	2+	3+	0	1+	2+	1+	2+	3+
3	9	8	0	0	17	0	6	8	3
4	8	5	0	0	6	7	1	8	4
5	0	3	0	0	0	3	0	0	3
6	0	1	0	0	0	1	0	0	1







17 patients (50%) had 1 + grading of fibrosis and 17 patients (50%) had 2+ grading of fibrosis, patients who received more than 4 cycles had fibrosis 2+.
23 patients (67.64%) had 1 + grading of necrosis and 11 patients (32.35%) had 2+ grading of necrosis. Patients who received more than 4 cycles had necrosis 2+
10 patients (29.41%) had 1+ grading of inflammation, 14 (41.17%) patients had 2+ grading of inflammation and 10 (29.41%) patients had 3+ grading of inflammation. Patients who received more than 5 cycles had inflammation 3+.
Hence our present study shows that when histopathological parameters were considered all parameters were more for patients who received more than 4 cycles.
None of the patients had psammoma bodies in their specimen
In our study 1 patient had recurrence and the histopatholgical parameter fibrosis was 1+.
20 (58.82%) patients had 1+ residual tumor and 14 (41.17%) had 2+ residual tumor, when mean difference between the pre and post NACT CA-125 levels were measured, it was more in patients under 1+ residual tumor group which was 2713, while in 2+ residual tumor group was 343, hence our study assumes that reduction in CA-125 levels were correlated to reduction in tumor. The more the difference the less residual tumor was noted in the specimen.

Adjuvant Chemotherapy in Post-Operative Patients

This pie chart shows that following surgery 6 patients (17.6%) received 3 cycles of adjuvant chemotherapy, 9 patients (26.5%) received 4 cycles, 9 patients (26.5%) received 5 cycles, and 10 patients (29.4%) received 6 cycles of adjuvant chemotherapy.

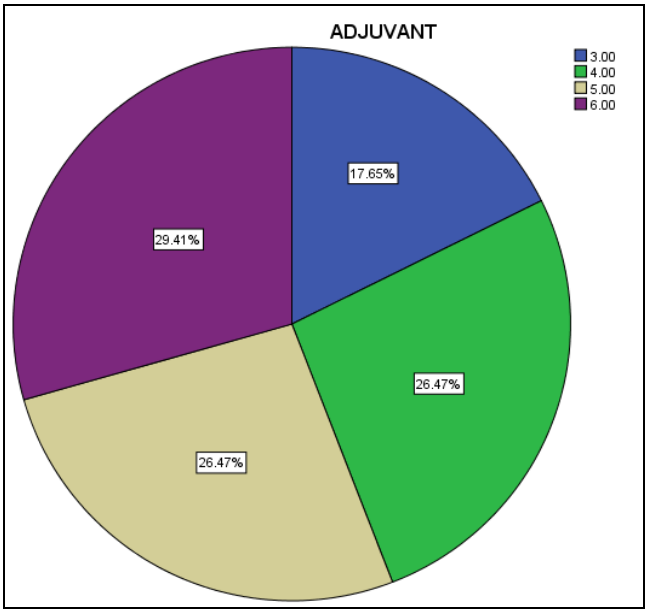


Fig 3: Pie chart representing adjuvant chemotherapy

Histological Types of Tumors

This pie chart shows that most no of patients 23 (67.6%) had serous type of tumor on histopathological evaluation, 8 patients (23.53%) had mucinous type and 3 patients (8.82%) had clear cell type.
Higher incidence of serous carcinoma was seen in our study group.

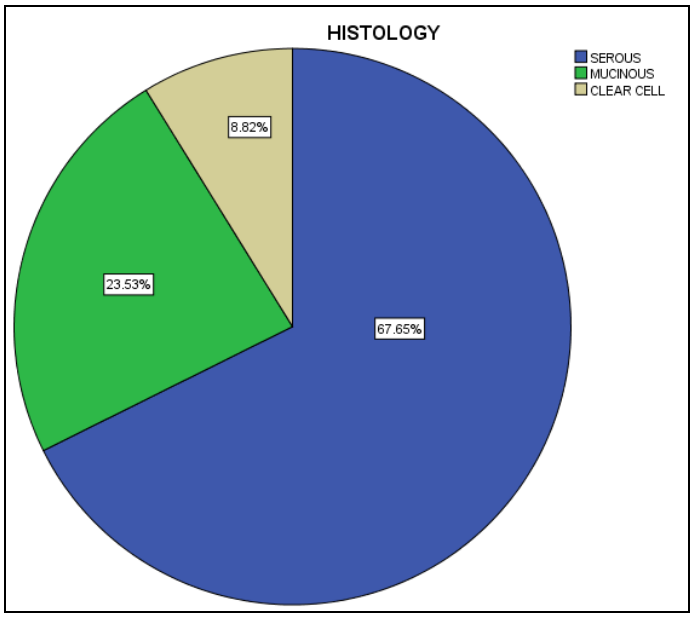


Fig 4: Pie chart representing histological types of Tumors

Discussion

Primary surgery followed by platinum based chemotherapy is the standard management of ovarian cancer,

But in our study we have observed that NACT followed by interval debulking and then adjuvant chemotherapy for advanced stage of ovarian cancer has reduced the tumor burden during the surgery which helps in complete surgical resection of tumors

Thirty four cases of epithelial ovarian cancer patients were studied in K S Hegde Hospital over a duration period of two years.

In my study the mean age of patients were 51.32± 9.66 and the range varied from 29- 70 years.

Similar results were shown in my study conducted by R Jha [5] in the year 2008.

Similar study done in western countries also showed that most common age group of malignant ovarian tumor is between 50 and 70 years the youngest patient in our study was 29 years of age (Mucinous cysadeno carcinoma). The oldest was 70 years of age with malignant ovarian tumor (Serous cystadenocarcinoma)

Table 11: Comparison of parity distribution of malignant ovarian tumors

Study	Nullipara	Para 1	Para 2	Para 3	Para 4	Para 5 and above
Booth M *et al* (1989)[6]	59	43	63	37	13	20
Kanthikar *et al* (2014)[7]	10	1	1	-	-	-
Shah Vaidya *et al* (1990)[8]	6	3	2	2	2	1
Present study	3	3	9	9	6	4

From the previous studies it has been shown that multipairty reduces the risk of malignancy, risk of reduction was around 50% [9] and nullparity incrases the risk of mailgnancy, but our study failed to show the relationship between parity and and incidence of the disease primarily due to less number of cases

Our study had only 3 (8.82%) nulliparous patients while most of the patients were para2 and para3, having 9 (26.47%) patients under each group.

Parity is one of the well-established protective factor for ovarian cancer. A study done by Hankinson and Danforth in 2006, showed that when compared with nulliparous women, women with atleast one full term pregnancy had a lower risk of ovarian carcinoma.

When other studies were analysed conducted by Booth M *et al*, Kanthikar *et al* and Shah *et al*, there was a high incidence of ovarian malignancy in nulliparous women when compared with age matched parous women group [6-8].

Table 12: Radiological response rate to chemothearapy (Recist criteria)

Response	Mazzeo *et al* (2003) [10]	Sonia *et al* (2010) [11]	Present study (n=34)
Complete response	1	17	0
Partial response	33	27	31 (91.17%)
Stable disease	8	6	2 (5.88%)
Progressive disease	3	0	1 (11.76%)

When radiological response rate to chemotherapy was compared with study done by Mazzeo *et al* in 2003 and Sonia *et al* in 2010 and present study, it showed that majority of patients were under Partial response 33, 27 and 31 respectively [10].

When patients with stable disease were considered Sonia *et al*, mazeo *at al* and the present study showed that there were 8 patients, 6 patients and 2 patients respectively [10, 11].

When patients with progressive disease was considered mazzeo *et al* had 3 patients, while present study had only 1 patient.

when patients with complete response were compared it showed that Mazzeo *et al* and present study was least and similar In the group of patients who showed response to chemotherapy were sixteen patients had 3 cycles of NACT, 12 patients had 4 cycles of NACT and 3 patients had 5 cycles of NACT. Two patients (5.88%) had progressive disease; one received 3 cycle and other 4 cycles respectively. One patient (2.94%) had stable disease who received 6 cycles of NACT Patients who received 3 cycles of NACT showed more incidence of partial response than patient who received 6 cycles of NACT who had stable disease.

Table 13: Correlation of reduction in Ca-125 and residual tumor size

Residual tumor	Mean reduction of CA-125
NO Residual Tumor (26)	99.11
<1cm (5)	35.66
≥1cm	344

In the present study when mean reduction of CA-125 and residual tumor was studied in no residual tumor group it was 99.11, <1cm residual tumor mean reduction was 35.66 and ≥1cm residual tumor mean reduction was 344.

Matsuhashi *et al* conducted a study where they studied on CA-125 levels after NACT in patients with stage III/IV ovarian cancer undergoing IDS (n=60) according to residual disease [12].

Table 14:

Post NA CT CA-125 levles (U/mL)	Complete /optimal IDS (n=38)	Suboptimal IDS (n=22)	Total
<35	32	9	41
>100	6	13	19

Hence the study concluded that post NACT CA-125 levels of less than 35 U/ML can be used as prognostic factor. When post NACT CA-125 was less than 35 had larger number of patients under complete IDS than patient who had post CA-125 more than 100.

Table 15: Correlation of number of NACT cycles and histopathological parameters

Study	No of Nact cycles	Fibrosis			Necrosis			Inflammation		
		1+	2+	3+	0	1+	2+	1+	2+	3+
Present study	3	9	8	0	0	17	0	6	8	3
	4	8	5	0	0	6	7	1	8	4
	5	0	3	0	0	0	3	0	0	3
	6	0	1	0	0	0	1	0	0	1
Le *et al* [13]	3	33	18	11	32	3	27	45	14	3
Samrao *et al* [14]	3 - 4	29	16	27	40	19	8	36	31	0

Conclusion

In advanced stage ovarian cancer NACT followed by interval cytoreduction has been mentioned as the standard of care in most of the clinical trials and also in the recently updated guidelines formulated by national comprehensive cancer network.

We in our present study could also come to the conclusion that NACT was definitely useful in reducing the tumor burden and tumor volume, it also helped in attaining optimal cytoreduction which is one of the most important independent prognostic factor as far as overall survival is concerened.

In our study the response to NACT was assessed both clinically, biochemically and radiologically using RECIST criteria 2.0.

Since overall sensitivity of clinical assessment was only 50 %, most of our decision making during the course of the study was based on biochemical and radiological response.

Serum CA-125 as tumor marker was definitely valuable in assessing the response to NACT in almost all patients.

Reduction in CA-125 level helped us in planning the timings of interval cytoredution. Interval cytoreduction was done in patients who had a maximal reduction in serum CA-125 levels.

We could obtain optimal cytoreduction in all the patients in whom there was a radiological response evaluated through CT scan.

Our study also showed a correlation between reduction in serum CA-125 levels and histopathological parameters.

In patients who had significant reduction in CA-125 there was minimal residual disease on histopathological examination.

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Conflict of interest: None declared

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

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