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Original Research Article

Outcome of advanced epithelial ovarian cancer: a tertiary care centre study

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ABSTRACT

Background: Ovarian cancer is the fourth most common cancer in Indian women with an incidence of 4.9 cases per 100,000. Epithelial ovarian cancer is a silent killer disease as it presents at an advanced stage with minimal signs and symptoms.
Methods: It is a type of research article. The present study was conducted in Department of Obstetrics and Gynecology, Cama and Albless Hospital, Mumbai, Maharashtra, India, from a period of January 2018 to July 2019, during which 53 cases of EOC were studied.
Results: Out of 53 cases of EOC, 45 cases were advanced stage EOC, they were either operated as PDS-ACT or NACT-IDS.
Conclusions: NACT is recommended wherein optimal cytoreduction appears unlikely, or in patients where upfront surgery is high risk and extensive causing high morbidity post-surgery. Places where there is non-availability of special surgical expertise and hospital resources, there too NACT-IDS is recommended.

Keywords: Epithelial carcinoma ovary, NACT, Debulking surgery, Chemotherapy, ACT

INTRODUCTION

Ovarian cancer is the fourth most common cancer in Indian women with an incidence of 4.9 cases per 100,000 (GLOBOCAN 2012).[1]

Ninety percent of ovarian cancers are derived from coelomic epithelium. Germ cell tumors account for 5% of ovarian cancers and sex cord-stromal tumors approximately 7%.[2] About 70% of patients with EOC present with advanced disease, as a result of the lack of any satisfactory screening test and specific symptoms.[3]

Complete resection during cytoreductive surgery is the most important independent prognostic factor in advanced EOC. Survival is inversely related to the residual disease after surgery.[4,5] Although the aim of cytoreductive surgery should be leaving no gross residual disease, there is still a significant benefit in trying to achieve "optimal" residual disease status (i.e., <1 cm), because such patients have a 10 months longer median OS, compared to patients with suboptimal residual disease.

The first line treatment for EOC is primary debulking surgery (PDS) followed by adjuvant chemotherapy (ACT) However, patients with advanced ovarian cancer who do not achieve optimal debulking at the end of primary cytoreductive surgery do not benefit from this procedure and are likely to experience morbidity associated with extensive surgery.

Neoadjuvant chemotherapy (NACT) before cytoreductive surgery has been extensively studied in patients who are unlikely to attain optimal cytoreduction or are poor surgical candidates.[6,7]

The decision whether a patient with advanced ovarian carcinoma (Stage IIIC or IV) is a better candidate for primary or interval cytoreduction depends on many factors including the patient's performance status, surgeon's experience, and computed tomography (CT) imaging, which provides information about the extent of the disease and whether optimal cytoreduction is likely.[8]

Being a tertiary cancer care center, majority of ovarian cancer patients presenting to our hospital have advanced disease and/or are in poor performance status and therefore unsuitable for upfront surgery. The aim of this study was to review the outcomes of advanced EOC patients treated with NACT protocol at out center.

The objectives are to study the incidence of ovarian neoplasm and to compare the outcome of primary debulking surgery (PDS) with adjuvant chemotherapy (ACT) vs neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS). To know the progression free survival in both arms of the study.

METHODS

This was a prospective observational analysis conducted at Cama and Allbless Hospitals, Mumbai from January 2018-July 2019.

Inclusion criteria

Inclusion criteria for the study were age between 40-70 years females with a histopathological confirmed report of locally advanced/inoperable/borderline operable epithelial carcinoma ovary; with a performance status of 0 to 2.

Exclusion criteria

Patients with early stages /operable stages of carcinoma ovary, recurrent carcinoma ovary were excluded from the study. Also, patients with a poor performance status weren't included in this study

Method

Over a period of 1.5-year patients who were in poor general condition and/or not likely to be debulked optimally were offered NACT (Paclitaxel and Carboplatin) followed by interval cytoreduction and then adjuvant chemotherapy.

Optimal cytoreduction was defined as no evidence of macroscopically visible residual disease or residual disease ≤1 cm. After the completion of primary treatment, patients were followed up 3-4 monthly, for a maximum of 8 months.

Thereafter. At each follow-up visit, a complete physical examination and serum CA-125 level was done. Imaging was advised in case patient presented with symptoms, or a rise in serum CA-125 levels.

Ethical approval was taken.

Statistical analysis

Statistical analysis was done using data filling excel sheet, using SPSS software and the difference with a p value of <0.05 was considered statistically significant.

RESULTS

In this study, between Jan 2018 to July 2019, 130 patients of ovarian pathology were assessed in our gynecological department. The diagnosis of Epithelial ovarian malignancy (EOC) was made in 53 patients, the others had either benign pathology or non-ovarian malignancy.Of the130 cases, 53 cases were of epithelial ovarian carcinoma, out of which 15.1% (n=8) belonged to the early stage (1 and 2) and 84.9% (n=45) were in the advanced stage.

Table 1: Stagewise distribution of epithelial ovarian cancer.

Stage	Noof cases	%
Stage 1 and 2	8	15.1%
Stage 3 and 4	45	84.9%

The most common stage at presentation was stage 3c.

Table 2: Stagewise distribution of advanced EOC.

Stage	No. of cases	%
Stage 3A	4	8.8%
Stage 3B	3	6.6%
Stage 3C	30	67%
Stage 4	8	17.78%

The histopathological characteristics of patients with advanced EOC (n=45).

Table 3: Histopathological characteristics of patients with advanced EOC.

High grade serous carcinoma	80%
Endometroid carcinoma	6%
Mucinous carcinoma	6%
Seromucous carcinoma	6%
Low grade serous carcinoma	2%

Sociodemographic profiles of the patients with advanced EOC revealed that 100% of the cases were from Maharashtra. 53% were from urban area whereas 47% patients were from rural area. The cases of advanced EOC were most common in the age group of 50-60 years. The

median age group was 56 years (range 40-70 years). Out of the patients, 30% were illiterate, 58% had received primary education, and 12% had received secondary education. Out of the 45 patients with advanced EOC, 11 cases were perimenopausal and 42 were postmenopausal. Most of the patients were of the parity P2L2.

4 patients out of 45 (8.8%) had a past history of carcinoma breast, with one patient having a concurrent family history of ca breast and ca ovary.

Most of the complaints were non-specific, distension of the abdomen was the most common complaint of an average duration of 2 months. Other symptoms included pain in abdomen, vomiting, weight loss, loss of appetite and vaginal bleeding. The initial ca -125 levels were varied with a wide range from serum level 35 to 11,680.

The 45 patients with advanced disease (n=45), 57% (n=27) women received NACT and the rest 43% (n=18) for PDS (primary debulking surgery). Of the women given NACT (n=27) from Jan 2018 to July 2019, 23 women have been operated with interval debulking surgery. The rest 4 had yet to be posted for surgery.

Table 4: NACT- IDS vs PDS.

	No. of cases	%
NACT-IDS	27	57%
PDS	18	43%

Most of the complaints were non-specific, distension of the abdomen was the most common complaint of an average duration of 2 months. Other symptoms included pain in abdomen, vomiting, weight loss, loss of appetite and vaginal bleeding. The initial ca -125 levels were varied with a wide range from serum level 35 to 11,680.

The women who were given NACT, 33% (n=9) had an ECOG of 0, 56% had an ECOG of 1 and 11 % (n=3) had an ECOG of 2. The most common ECOG status in the PDS group was 0. The median number of NACT cycles received before surgery was 4c (3c- 6c). NACT was given as a combination drug of paclitaxel + carboplatin, 3 weeklies. Carboplatin was given under AUC 4. The most common NACT dose limiting/ schedule prolonging side effect was febrile neutropenia.

3 patients out of the 27 treated with NACT (11.11%) had febrile neutropenia, requiring inj GM-CSF. Only one patient receiving PDS, 5.5% had febrile neutropenia.

100% of the women responded to the NACT. Post NACT CT scan as per RECIST 1.1 showed that 2 patients had complete response and the rest 25 patients had partial response.

Chemoresponse score was defined in our institutional hpr reports after June 2018. 10 cases of IDS (interval debulking surgery), post NACT, gave the following results.

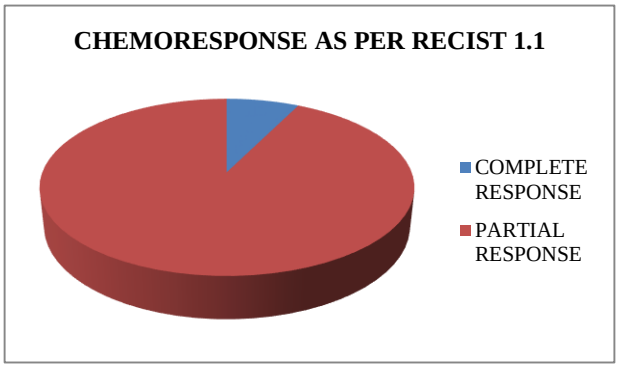

Figure 1: Chemoresponse post NACT as per RECIST 1.1.

Table 5: Chemoresponse score.

Chemoresponse score	
CRS3	20% (N=2)
CRS2	60% (N=6)
CRS1	20% (N=2)

The median time interval between the last chemotherapy in NACT and IDS surgery was 40.8 days (29 days-56 days). Of the 23 number of operated cases post NACT, optimal cytoreduction was achieved in 100% cases. R0 cytoreduction was achieved in 21 cases. In the PDS group (n=18), optimal cytoreduction was achieved in only 88% of the cases.

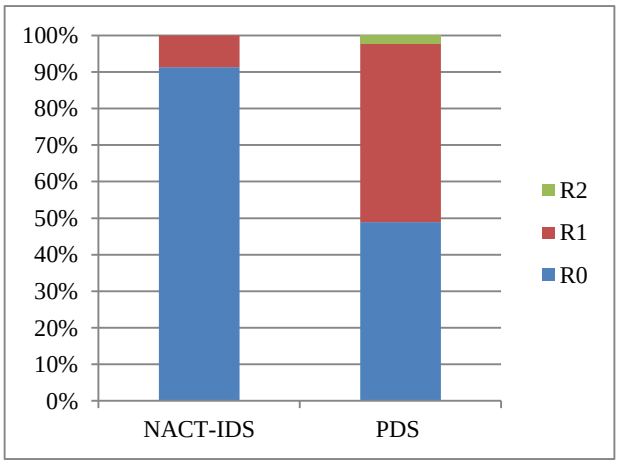

Figure 2: Resection status in NACT –IDS vs PDS.

Interval debulking surgery, post NACT caused a statistically significant cytoreduction compared to PDS (p-value = 0.004).

The most common postoperative complication overall was wound gape and blood loss (500-1000ml). the overall incidence of complications was higher in the PDS group. In the PDS group 72.2% patients requiring blood

transfusions and 22.2% patients having an extended hospital stay due to resuturing. In the NACT group, 13.04% patients required blood transfusions, 47.82% patients had resuturing.

The incidence of postoperative complications was higher in the PDS group and was statistically significant (p-value =0.01).

PDS was associated with a higher incidence of grade 3 blood loss.

Table 6: Grade of postoperative blood loss in NACT-IDS vs PDS.

	NACT-IDS	PDS
<500ml	3	1
500-1000ml	0	7
>1000 ml	0	5

The higher degree of blood loss was statistically significant. (p- value – 0.003).

The median postoperative stay was 12 days in the NACT-IDS group.

(S=4, at 95% CI, 12+/- 1.605). Range of 9-18days. Whereas in the PDS group the median postoperative stay was 18.4 days (S=1.46, at 95% CI, 18.4 +/- 0.6). Range of 13- 21 days. The median time interval between surgery and start of adjuvant chemotherapy was 35 days (28-42 days) in the NACT- IDS group, and 42 (30- 48days) days in the PDS group.

The NACT- IDS group received 3c- 4c of adjuvant chemotherapy of paclitaxel + carboplatin, 3 weekly. The PDS group received 6c of the adjuvant chemotherapy

Of the 23 patients operated in the NACT group, 22 patients have completed the 4 month follow up, of which one patient relapsed within 3 months of end of treatment and was started on 2nd line gemcitabine. 15 patients completed the 8 monthly follow up, of which 5 patients relapsed, three within 5 months (started on 2nd line gemcitabine), the other two at 8 and 9 months respectively and have been rechallenged with high dose carboplatin. In the PDS-ACT group, 18 cases were operated, 16 patients have completed the 4 monthly f/up, of which 5 patients relapsed in 2nd and 3rd months, of which three were started on liposomal doxorubicin and the two on 2nd line gemcitabine. 13 patients have completed the 8-month f/up with two relapses at 7 months and has been rechallenged with high dose carboplatin.

Table 7: Relapse rate in NACT-IDS vs PDS – ACT.

	NACT-IDS	PDS
4 months	1	5
8 months	5	2

The relapse rate in the PDS group was higher and statistically significant (p- value = 0.048).

Table 8: PFS at 8 months in NACT-IDS vs PDS.

	NACT-IDS	PDS
PFS at 8 months	74%	61.2%

The PDS- ACT group at 8 months PFS was 61.2%. Amongst the relapse group, the average PFS was 4.5 months (2 months- 7 months). The PFS in the NACT group at 8 months was 74%. Amongst the relapse group, the average PFS was (3 months – 9 months).

In the optimal cytoreduction case (n=39), 17.94% patients (n=7) relapsed with an average PFS OF 6.8 months. In the 2 patients of suboptimal cytoreduction, both patients relapsed at 2 months.

DISCUSSION

53% of women presenting to our center were from rural Maharashtra, of which 30% were illiterate. A similar study done at TATA cancer institute quoted a referral of 56% rural population and a 19% illiteracy rate.[13]

Majority of the women presented with higher birth order, the most common parity being P2L2, however nulliparity and not parity is a known risk factor for carcinoma ovary.[18]

The median age of women with EOC was 56 years. This is a decade younger than the median age reported in the Western literature.[1-3] The exact reason for this age difference is not known; however, this could be a reflection of the overall demographic profile of Indian population with a relatively younger population than the west or due to referral bias. The study at TATA cancer institute also found it to be 56 years of median age.[13]

8.8% of the patients had a positive past history or family history of ca breast and ca ovary. This is relatable to the literature which quotes 10% of ovarian cancer cases are hereditary.[1,2]

The most common symptom was distension of abdomen over an average duration of 2 months, which is what most of the literature quotes.[15-17]

The most common stage at presentation was stage 3c, with high grade serous carcinoma being the most common subtype, which is in accordance with all the literature reports.[1-3,13]

The median number of NACT cycles before interval cytoreduction was 4c. Bristow and Chi, in a meta-analysis of 835 patients undergoing interval cytoreduction, had reported that within the rate of 3-6 cycles, each incremental chemotherapy cycle was associated with a decrease in 4.1 months in median survival (P = 0.046).[9]

However no such association was found in the present study.

The median time interval between last chemotherapy and surgery was 40.8 days. The study conducted at TATA hospital, quoted 39 days.[13]

Of the 23 number of operated cases post NACT, optimal cytoreduction was achieved in 100% cases. R0 cytoreduction was achieved in 82.6%. In the EORTC trial, on comparing primary and interval cytoreduction, optimal cytoreduction (largest residual tumour ≤1 cm) was achieved in 80.6% patients after interval debulking.[6] Even in the study conducted at tata hospital 13 optimal cytoreduction post NACT was achieved in 81.5% cases.

In the PDS group, optimal cytoreduction was achieved in only 88% of the cases. The EORTC trial has quoted a optimal cytoreduction rate of 41.6%.[6,9] The reasons for this vast discrimination can be due to small scale of this study, inter surgeon reporting bias and histopathology report.

The median postoperative stay in the NACT vs PDS group was 12 days vs 18 days. And the time interval between starting of adjuvant chemotherapy was 35 days in the NACT group and 42 days in the PDS group. It means that NACT group patients could start treatment post-surgery a week earlier. In TATA the median postoperative stay was 5 days.[13]

Limitation of this study are its small sample size and many patients being lost to follow up, since most of them were referral cases from rural Maharashtra.

CONCLUSION

Sociodemographically rural Maharashtra needs more cancer care centres. there is need of more awareness of ovarian cancer symptoms.

Reviewing the overall result, NACT is recommended wherein optimal cytoreduction appears unlikely, or in patients where upfront surgery is high risk and extensive causing high morbidity post-surgery. Places where there is non-availability of special surgical expertise and hospital resources, there too NACT- IDS is recommended.

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

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