

Interval Debulking Surgery (IDS) in Advanced Ovarian Cancer - Immediate Surgical Outcomes and Optimal Cytoreduction Rate

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ABSTRACT

Introduction: In Indian women, ovarian cancer is the fourth most common cancer, out of which epithelial ovarian cancers are the most common and present in advanced stage. Women with other comorbidities and those who are unlikely to achieve optimal debulking at primary surgery, benefit from neoadjuvant chemotherapy (NACT) followed by interval cytoreduction, with lesser surgical morbidity and equal survival rates as compared to primary cytoreduction.

Material & methods: A 1 year retrospective study was conducted at tertiary care hospital situated in Bangalore from June 2018 to May 2019. Total 9 study participants who underwent interval debulking surgery following neoadjuvant chemotherapy were included in this study. Data was collected from hospital record using a pre designed questionnaire which had variables like age, stage of ovarian carcinoma at the time of diagnosis, number of NACT cycles that the study subjects underwent, blood loss, volume of residual disease, optimal cytoreduction rate, intraoperative complications and immediate surgical outcomes. Histopathological examination reports were collected and chemotherapy response score, grade and type of tumour were ascertained.

Results: Epithelial cancers constituted 100% (n = 10) of all cases. The mean age of the patients who underwent IDS following NACT was 52.22 ± 5 years ranging from 46 to 62 years. All cases presented at advanced stage with 3 (33.3%) being in Stage IIb, 4 (44.4%) being in Stage IIc and 2 (22.2%) being in Stage IV at the time of diagnosis. The median number of NACT cycles (paclitaxel + carboplatin) was 3. Optimal cytoreduction (residual disease <1cm) was

achieved in 77.7% cases. The median postoperative stay was 7 days.

Conclusion: High rates of optimal cytoreduction were achieved at interval cytoreductive surgery after NACT with acceptable surgical morbidity.

Keywords: Advanced ovarian cancer, Interval debulking surgery, neoadjuvant chemotherapy, residual disease, optimal cytoreduction

INTRODUCTION

Ovarian cancer is the 4th most common cancer in India amongst women with its incidence being 4.9 cases per 100,000.¹ The incidence of ovarian cancer is 3.4% worldwide and is responsible for 4.4% of deaths from cancer annually.²

About 90% of ovarian cancers have coelomic epithelial origin. Sex cord stromal and germ cell tumours account for 7% and 5% of ovarian cancer cases respectively. The types of epithelial ovarian cancers include high-grade serous carcinoma (70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%) and low-grade serous carcinomas (<5%).¹

Greater than 75% of women present in advanced stage of ovarian cancer that is Stage III or Stage IV as per International Federation of Gynaecology and Obstetrics (FIGO) staging of ovarian carcinoma and their 5-years survival rate is less than 30%.³ The foremost factors affecting the survival of women presenting with advanced ovarian

cancer are the extent of cytoreductive surgery and the amount of residual disease. Residual disease of more than 1 to 2 cm even after extensive surgery doesn't have much influence on survival rate. Interval debulking surgery (IDS) is done subsequent to a few cycles of platinum based systemic chemotherapy, known as neoadjuvant chemotherapy (NACT). IDS helps to achieve optimal resection and improved patient performance status by reducing perioperative morbidity.⁴ IDS was associated with lower morbidity, 33% mortality rate reduction and significantly increased median survival of 6 months compared to those who had not undergone this procedure.⁵

The following conditions are suggestive of unresectable advanced ovarian cancer requiring initial neoadjuvant chemotherapy⁴

- Large ascites (>500ml), large pleural effusion on CT scan
- Dense adhesions between bowel and omentum
- Omental disease extending to spleen
- Large diaphragm disease
- Large tumor nodules adherent to abdominal structures
- Carcinomatosis on small and large bowel
- Agglutination of bowel mesentery
- Two or more bowel resections
- Surface or parenchymal liver or porta hepatitis involvement

The objective of our study was to evaluate the immediate surgical outcomes and optimal cytoreduction rate of patients undergoing NACT followed by interval debulking surgery.

MATERIALS & METHODS

A retrospective observational study was conducted in a multispecialty tertiary care in Bengaluru, South India from June 2018 to May 2019. Purposive sampling was done to select the study participants. Total 9 study participants who underwent interval

debulking surgery following neoadjuvant chemotherapy were included in this study.

Our study included all women who were diagnosed with advanced ovarian cancer presenting in FIGO Stage III or IV and were deemed unfit for primary debulking surgery. The subjects underwent interval debulking surgery following neoadjuvant chemotherapy over the study period of 1 year.

Patients who were not willing to give consent and who did not undergo interval debulking surgery following neoadjuvant chemotherapy were excluded from the study.

Verbal consent was taken from the study subjects who were then interviewed over telephone. Data was collected from hospital record using a pre designed questionnaire which had variables like age, stage of ovarian carcinoma at the time of diagnosis, CA-125 values – pre NACT and pre surgery, number of NACT cycles that the study subjects underwent, intraoperative findings and blood loss, volume of residual disease, optimal cytoreduction rate, intraoperative complications and immediate surgical outcomes including number of blood transfusion required postoperatively, duration of ICU and hospital stay. Histopathological examination reports were collected and chemotherapy response score, grade and type of tumour were ascertained.

The data collected was tabulated on Microsoft Excel sheet and analysed using SPSS Version 25. The categorical variables were collated in frequency and percent and the continuous variables were calculated as mean \pm standard deviation.

RESULT

There were total of 9 ovarian cancer cases in the study period of 1 year who underwent NACT followed by IDS. The total number of ovarian cancer cases presenting in the facility in the study period were 52 with the incidence of patients undergoing NACT followed by IDS being 17.3%.

Table – 1 shows the distribution of clinical characteristics of study subjects. The mean age of the patients who underwent IDS following NACT was 52.22 ± 5 years ranging from 46 to 62 years. All cases presented at advanced stage with 3 (33.3%) being in Stage IIIb, 4 (44.4%) being in Stage IIIc and 2 (22.2%) being in Stage IV at the time of diagnosis. The mean pre and post NACT CA-125 values were 6311.37 and 150.73 mIU/ml respectively. The average number of platinum based NACT cycles that the study subjects went through were 4.11 ± 1.4 cycles ranging from three to six cycles.

As per Table – 2, the average amount of blood loss was 488.89 ± 220.47 millilitre ranging from 300 ml to 1000 ml in case where there was inferior vena cava injury. The mean number of intraoperative and postoperative packed cell transfusion required by the patient collectively was 1.6 ± 0.82. The mean operative time was 454.44 ± 138.12 minutes. Intraoperatively residual disease of more than one centimetre was present in 2 (22.2%) cases with optimal cytoreduction that is no visible disease or residual disease less than one centimetre, in 7 (77.7%) cases. Hence, optimal cytoreduction rate was 77.7%. Intraoperative complications included bowel injury in 2 (22.2%) and blood vessel (inferior vena cava) injury in 1 (11.1%) cases while resection of the disease. The mean numbers of days of stay in intensive care unit (ICU) were 1.89 ± 1.1 days ranging from one day to four days. The

average hospital stay was 7.44 ± 2.6 days ranging from four to twelve days.

Table – 3 shows distribution of histopathological findings in the case subjects where all cases were epithelial ovarian cell carcinoma with 8 (88.8%) cases being serous cell variant and 1 (11.1%) case being clear cell carcinoma. Histological grading of tumour revealed 8 (88.8%) cases being high grade tumour and 1 (11.1%) case having no residual disease on histopathological examination. Chemotherapy response score (CRS) assesses histological effect of NACT on the tumour cells and is significant for overall survival and relapse. CRS 1 was found in 2 (22.2%) cases in which there was no or minimum response to NACT as viable tumour cells were found with no or minimal regression and fibroinflammatory changes making it difficult to differentiate between regression or inflammatory cell infiltration. CRS 2 was found in 6 (66.6%) cases which signified appreciable tumour response but viable tumour cells were also identified amidst regression associated fibroinflammatory changes. CRS 3 was found in 1 (11.1%) case which meant that complete chemotherapy response was present with no residual tumour cells.

Table – 1 Distribution of clinical characteristics of the study subjects

| Characteristics | | N=9 |
|--------------------------------|-------------|----------------------|
| Age (in years) | | 52.22 ± 5 (46-62) |
| FIGO staging of ovarian cancer | IIIa | 0 |
| | IIIb | 33.3% (3) |
| | IIIc | 44.4% (4) |
| | IV | 22.2% (2) |
| CA125 (in mIU/ml) | Pre NACT | 6311.37 (393-25,134) |
| | Pre Surgery | 150.73 (13.2-400) |
| Number of NACT cycles | | 4.11 ± 1.4 (3-6) |

Table – 2 Distribution showing surgical outcome of the study subjects

| Variables | | N=9 |
|---|---------------------|----------------------------|
| Operating time (in minutes) | | 454.44 ± 138.12 |
| Residual Disease | | 22.2% (2) |
| Optimal Cytoreduction Rate | | 77.7% (7) |
| Intraoperative complication | Bowel injury | 22.2% (2) |
| | Bladder injury | 0 |
| | Ureter injury | 0 |
| | Blood vessel injury | 11.1% (1) |
| Blood loss (in millilitres) | | 488.89 ± 220.47 (300-1000) |
| Blood transfusion (no. of packed cells) | | 1.6 ± 0.82 (0-2) |
| ICU stay (in days) | | 1.89 ± 1.1 (1-4) |
| Hospital stay (in days) | | 7.44 ± 2.6 (4-12) |

Table – 3 Distribution showing histopathological findings in study subjects

| Histopathological Variables | | N=9 |
|-----------------------------------|----------------------|--------------------------|
| Chemotherapy response score (CRS) | 1 | 22.2% (2) |
| | 2 | 66.6% (6) |
| | 3 | 11.1%(1) |
| Histological grade of tumour | | 88.8% high grade |
| | | 11.1% no residual tumour |
| Type of tumour | Serous Carcinoma | 88.8% (8) |
| | Clear cell Carcinoma | 11.1% (1) |

DISCUSSION

The mean age of the patients who underwent IDS following NACT was 52.22 ± 5 years ranging from 46 to 62 years. This was similar to findings of Vanderburg M et al⁶ where the mean age of presentation of women in advanced ovarian cancer was 59 years.

The optimal cytoreduction rate in present study was 77.7%. This was similar to optimal cytoreduction rate of 75.6% in study conducted by Georgeena P et al⁸. It was found to be 81.5% in patients undergoing IDS preceded by NACT in the study conducted by Maheshwari A et al¹. The optimal cytoreduction rate was less in study conducted by Ghisoni E et al³ where it was 69.8% for the same procedure. In a survey conducted by Iavazzo C et al⁹, 72% of the participants agreed that the first intervention in patients presenting with advanced ovarian cancer should be NACT followed by IDS to reduce the morbidity and increase the optimal cytoreduction rate.

All cases presented at advanced stage with 3 (33.3%) being in Stage IIIb, 4 (44.4%) being in Stage IIIc and 2 (22.2%) being in Stage IV at the time of diagnosis which was similar to study conducted by Ghisoni E et al³ where maximum patients presented at advanced stage. 15% presented in stage IIIb, 62.5% in stage IIIc and 12.9% in stage IV. The average number of platinum based NACT cycles that the study subjects went through were 4.11 ± 1.4 cycles ranging from three to six cycles in this study which was similar to study done by Medina-Franco H et al⁷ where the average number of platinum based NACT cycles received by the study subjects were 3. In study conducted by Martín-Cameán M et al¹⁰, it was found that with each chemotherapy cycle, there was decrease in 40.1 months of

survival. Hence, optimum of 3 cycles of chemotherapy prior to IDS was recommended and 3 cycles of chemotherapy after the surgery.

The mean operative time was 454.44± 138.12 minutes in present study. As compared to study conducted by Rozenowicz et al¹¹, the mean operating time was 240 minutes ranging from 200 to 420 minutes. The mean number of intraoperative and postoperative packed cell transfusion required by the patient collectively was 1.6 ± 0.82 in this study which was similar to number of blood transfusion in study conducted by Rozenowicz et al¹¹ ranging from zero to four, average being two transfusions. The mean number of days of hospital stay in present study was 7.44±2.6 (4-12) days which was similar to findings in study conducted by Rozenowicz et al¹¹ where average number of hospital stay was 7 days ranging from 6 to 9 days.

Intraoperative complications included bowel injury in 2 (22.2%) and blood vessel (inferior vena cava) injury in 1 (11.1%) cases while resection of the disease. The intraoperative complication occurred in only 3 (33.3%) cases which signified less perioperative complication and morbidity. The mean numbers of days of stay in intensive care unit (ICU) were 1.89 ± 1.1 days ranging from one day to four days. Similarly in a meta-analysis conducted by Yang L¹², it was found that NACT followed by IDS was associated with less perioperative complications with respect to infection, gastro intestinal fistula and perioperative death within 28days after surgery.

In a meta-analysis by Zeng L¹³, it was concluded that NACT followed by IDS had increased rate of optimal cytoreduction but had inferior overall survival rate as

compared to patients undergoing primary cytoreduction. This was attributed to better performance status and lesser extent of tumour found in subjects undergoing primary cytoreductive surgery. One drawback that was incurred during interval cytoreductive surgery after NACT was widespread fibrosis due to chemotherapy. The postoperative residual fibrosis, containing viable tumour cells, promoted chemotherapy resistance post-surgery. Similar problem was faced in one (11.1%) case in present study whose CRS score came out to be 1 and had complication of bowel injury.

CONCLUSION

Optimal cytoreduction rate was found to be 77.7% in patients undergoing IDS after NACT. Those who are unfit for primary cytoreduction surgery should be given option of NACT-IDS. Residual disease <1cm was found in only 22.2% cases. IDS was associated with less morbidity and intraoperative complications happened in only 33.3% cases in present study. There was less blood loss and need for transfusion was low. 66.6% cases had CRS of 2 which indicated appreciable chemotherapy response in histopathological examination of the specimen after surgery. However more studies needs to be done for determining the effect of CRS on median survival rate post-surgery. 100% cases in this study belonged to epithelial ovarian cancer which was highly sensitive to platinum based chemotherapy. Also there was no immediate postoperative mortality noted in this study. The limitation of this study is that due to small study period, disease free interval, median survival rate and recurrence couldn't be evaluated.

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