

## Primary debulking surgery versus neo-adjuvant chemotherapy in stage III/IV ovarian cancer: Comparison of perioperative morbidity and survival data in Pakistani women

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### Abstract

**Objective:** To compare the peri-operative morbidity and survival rates between ovarian cancer patients treated with two different approaches.

**Methods:** The retrospective study was conducted at Aga Khan University Hospital, Karachi, and comprised data related to patients with advanced stage ovarian carcinoma treated between 1999 and 2008. Medical records were reviewed and relevant demographic, clinical, surgical, pathologic and follow-up information was acquired. Progression-free survival and overall survival rates were compared between patients who underwent primary debulking surgery and those who had received neo-adjuvant chemotherapy before surgery. SPSS 19 was used for statistical analysis.

**Results:** Of the total 118 patients, 78(66%) had undergone primary debulking surgery and 40(34%) had received neo-adjuvant chemotherapy. The mean age and pre-operative carcinoma antigen-125 level were similar. The debulking group had 74(94.8%) patients with stage 3, and 4(5.1%) patients with stage 4 disease, while the other group had 32(80%) and 8(20%) with stage 3 and 4 respectively. The frequency of optimal debulking was 42(56.8%) in the former group against 27(79.4%) in the latter ( $p=0.01$ ). Duration of surgery, estimated blood loss >1500ml and stay at the intensive care unit were not statistically different ( $p>0.05$ ). Rate of Urinary tract, bowel injury and bowel resections were also similar. There was no difference in the progression-free survival in both groups ( $p>0.05$ ).

**Conclusions:** Neo-adjuvant chemotherapy followed by interval debulking produced comparable survival rates and peri-operative complications.

**Keywords:** Ovarian epithelial cancer, Chemotherapy, Gynaecological surgical procedure, Survival analysis. (JPMA 65: 306; 2015)

### Introduction

Ovarian cancer is a disease of late diagnosis mainly because of its initial vague and non-specific signs and symptoms. The lack of an effective early detection/screening test is another dilemma contributing to this unfortunate fate.<sup>1,2</sup>

Usually women come to know about the disease when it has already spread to upper abdomen and distant areas.<sup>3</sup> Stage III or IV is reached in 70% by the time of diagnosis. At this stage the survival rate is as low as 10%. If the disease can be diagnosed earlier (stage I or II), the survival rate can be improved up to 80-95%.<sup>2,3</sup>

Currently the standard treatment of advanced ovarian cancer (stage III/IV) is primary debulking surgery (PDS) followed by chemotherapy. Debulking surgery typically involves performing a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO), complete omentectomy and resection of any metastatic disease.

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Resectibility of disease depends on the skills of the surgeon and the extent of disease. Optimal cytoreduction is difficult if there is an extensive disease involving upper abdomen or the under-surface of diaphragm. This kind of extensive surgical resection increases the morbidity rate but it has been proved in various studies that optimal cytoreduction is the most important prognostic factor for the survival of patients.<sup>4-7</sup>

The second option is to give neo-adjuvant chemotherapy (NACT), followed by surgery. This is a unique therapeutic approach for the extensive disease in which complete surgical resection is not possible initially either due to technical difficulty or because of patient's medical comorbidities.<sup>8</sup>

NACT significantly reduces the tumour burden before surgery and allows an easier and optimal cytoreduction. It also decreases the chances of morbidity and amount of blood loss of wide surgical resections and hence reduces intensive care unit (ICU) and hospital stay.<sup>4,9-12</sup>

The results of European Organisation for Research and Treatment of Cancer (EORTC) randomised trial showed

similar overall survival and progression-free survival when NACT was compared with standard debulking surgery. The morbidity was found lower in the NACT group, and it was concluded that NACT was an alternative to standard debulking surgery.<sup>2,13</sup>

The current study was planned to compare the results of these two treatment modalities in Pakistani women with advanced ovarian cancer. It is speculated that there is a socio-economic difference and, hence, there is an effect on the nutritional status of these women compared to their western counterparts. We compared the peri-operative morbidity of patients with ovarian cancer who underwent primary debulking surgery versus those who had received NACT followed by surgery, and compared the survival rate between the two treatment groups.

### Patients and Methods

The retrospective study was conducted at Aga Khan University Hospital, Karachi, after approval by the institutional ethics committee, and comprised data related to patients with advanced stage (stages III and IV) ovarian carcinoma treated between 1999 and 2008. Patients with early stage ovarian cancer, synchronous primaries, non-epithelial ovarian cancers and those with recurrence of ovarian cancers were excluded.

Patients in both the groups had received intravenous (IV) carboplatin and taxol-based chemotherapy. All patients had interim evaluation after 3-4 cycles of treatment for eligibility of surgery.

The decision to treat patient with PDS or NACT was at the discretion of tumour board panel comprising gynaecological oncologist and medical oncologist. The decision regarding primary treatment for a particular patient was based on factors including World Health Organisation (WHO) functional status of the patient,<sup>14</sup> medical comorbid, and whether or not disease was resectable at the time of presentation. At the study site, this required baseline imaging like computed tomography (CT) of the chest, abdomen and pelvis to determine if the disease was resectable or not. Unresectable disease was defined as: diffuse and/or deep infiltration of the small bowel mesentery; diffuse carcinomatosis involving the stomach and small or large bowel; infiltration of the duodenum and/or parts of the pancreas; and involvement of the liver parenchyma.

Standard debulking surgeries for both groups included a TAH, BSO, omentectomy, resection of enlarged pelvic/para-aortic lymph node and resection of implants, if any. All patients in the NACT group had their diagnosis confirmed pathologically by cytological or tissue biopsies before

starting chemotherapy. Serial physical examination, carcinoma antigen (CA)-125 measurement and CT imaging were used to assess treatment response at regular intervals.

Optimal cytoreduction was defined as either no residual disease or residual disease less than 1cm in maximal dimension at the end of the surgery. The international Federation of Gynaecologists and Obstetricians (FIGO) staging system<sup>15</sup> were used for disease classification. Medical records for all patients were reviewed and relevant demographic, clinical, surgical, pathologic and follow-up information was acquired. Progression-free survival and overall survival were compared between the two treatment groups. The parameters of peri-operative morbidity, including duration of surgery, estimated blood loss, special care stay along with surgical complications like bladder and bowel injury/resection and postoperative complications like infections and thromboembolism were also compared between the two groups.

SPSS version 19 was used for data recording and analysis. Categorical variables were compared using Chi square test. Survival analysis was generated using Kaplan Meier Survival curves. In descriptive statistics, means and standard deviations (SDs) were calculated for continuous normally distributed variables and median with range for non-normal distributions. Frequency and proportions were calculated for categorical variables. Pearson's chi-square or Fisher exact test was used to analyse the association of clinic-pathological characteristics. Continuous variables were analysed using the student T test. All median and life tables were calculated using the product-limit estimate and curves were compared using log-rank test.  $P < 0.05$  was considered statistically significant.

### Results

Of the total 118 patients, 78(66%) had undergone PDS and 40(34%) had received NACT. The mean age and pre-

**Table-1:** Demographic and clinical characteristics.

Characteristics	PDS(n =78) 66%	NACT (n=40) 34%
Mean age (years)	50.99±13.0	52.45±11.3
<b>Stage n(%)</b>		
III	74(94.8)	32(80)
IV	4 (5.1)	8 (20)
<b>Histology n(%)</b>		
Serous	48(72.7)	26 (89.7)
Mucinous	4(6.1)	1 (3.4)
Endometrioid	11(16.7)	2 (6.9)
Clear cell	2 (3)	0
Ca-125 (Mean) IU/ml	1954±2762.4	1909± 2486.4

PDS: Primary debulking surgery  
NACT: Neo-adjuvant chemotherapy.

operative CA-125 level were similar (Table-1). The debulking group had 74(94.8%) patients with stage 3, and 4(5.1%) patients with stage 4 disease, while the other group had 32(80%) and 8(20%) with stage 3 and 4 respectively. The median number of neo-adjuvant cycles was 6. Papillary serous carcinoma was the most common histologic type in 48(72.7%) in PDS group and 26(89.7%) in NACT group.

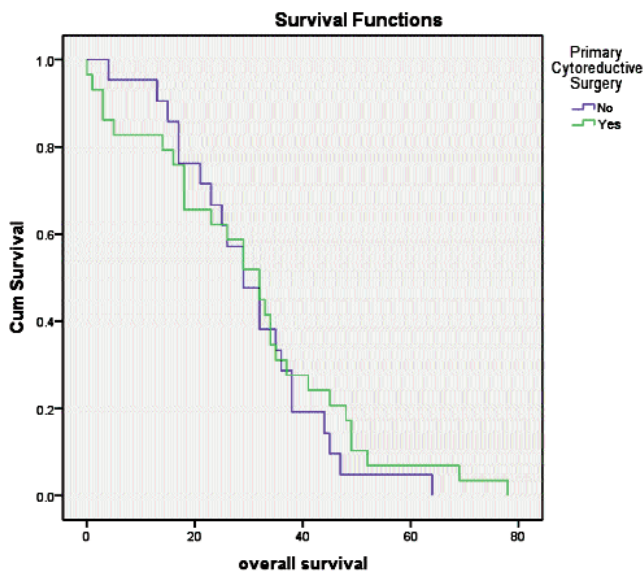
Duration of surgery, estimated blood loss >1500ml and stay at the intensive care unit were not statistically different ( $p>0.05$ ) (Table-2). Rate of Urinary tract, bowel injury and bowel resections were also similar. There was no difference in the progression-free survival in both groups ( $p>0.05$ ). The frequency of optimal debulking was 42(56.8%) in the former group against 27(79.4%) in the latter ( $p=0.01$ ).

Median survival outcome of NACT was 30 months compared to 32 months in the oDS group. Similarly, there

**Table-2:** Peri-operative parameters and intra/postop complications.

Characteristics	PDS	NACT	P value
Mean duration of surgery (min)	222±185.3	222±196.6	0.99
Mean Estimated blood loss (ml)	848±467.5	874±517.3	0.86
Blood loss > 1500 ml (%)	10(13.5)	5(13.5)	0.66
Mean Special care stay (days)	2.5±2.16	2.89±3.7	0.56
Bowel resection n (%)	12(15)	5(12)	0.67
Urinary tract injury*	4 (3.12)	1(0.4)	0.5
Optimal debulking n (%)	42(56.8)	27(79.4)	0.01*

\*Association was analysed using fisher exact test.



**Figure:** Comparison of overall survival.

was no difference in the progression-free survival in both the groups (Figure).

## Discussion

The goal of surgery for epithelial ovarian carcinoma is complete cytoreduction of tumour. The volume of the residual disease after cytoreduction is inversely proportional to the survival of the patient which has been confirmed by meta-analysis of over 6000 patients.<sup>5,6,16</sup> There is a general consensus that suboptimal cytoreduction provides no survival advantage to women with advanced ovarian cancer, so the aim should be optimal cytoreduction. Although its achievement largely depends on surgeon's expertise and selected patient population, but it is at the expense of increased risk of peri-operative morbidities.<sup>17,18</sup>

The Gynaecologic Oncology Group (GOG) defines optimal debulking/cytoreduction as leaving residual disease of less than 1cm in maximum diameter; whereas complete cytoreduction means no residual disease or total macroscopic clearance. This may involve extensive and aggressive surgical procedures leading to increased blood loss, operating time and amount of blood transfused.<sup>19</sup>

For last 30 years the gold standard of treatment for epithelial ovarian carcinoma is debulking surgery followed by adjuvant chemotherapy, but now different management strategies have evolved, especially for those who are not medically fit for extensive surgery or when the disease has spread widely. In these patients, debulking surgery is performed once they have completed three to six cycles of NACT.

A number of studies were done to compare the outcome of primary debulking followed by chemotherapy or NACT followed by debulking. Chemotherapy or Upfront Surgery (CHORUS), EORTC and some other trials have also compared these two management strategies and have shown similar survival rates in both groups with lesser morbidities in patients with NACT followed by debulking surgery.<sup>2,13</sup>

On the other hand some studies have shown correlation between NACT and longer survival.<sup>20,21</sup>

In our study the demographic details of both groups were comparable. Intra-operative and post-operative parameters, including estimated blood loss and ICU stay were also similar in both the treatment groups as well as in previous studies.<sup>4,21,22</sup>

The optimal cytoreduction rates achieved in our study groups were 56.8% in PDS versus 79.4% in NACT which was significant and comparable with other studies.<sup>9,23</sup>

Despite this difference in optimal cytoreduction, the pre-operative CA-125 level in our study was similar in both groups.

Our study did not show any difference in the survival rates between the two treatment groups. Extensive upper abdominal dissections were not routinely performed in our setup which could be one of the limitations of our study for not showing any survival benefit.

## Conclusion

NACT followed by interval debulking gave better chance of optimal debulking, comparable survival rates and peri-operative complications. It can be safely considered in a select group of patients with poor functional status, medical comorbidities and unresectable disease at the time of presentation.

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