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Clinicopathological Factors Predicting Survival in Women with Advanced Ovarian Cancer Treated with NACT Followed by IDS - A Retrospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author MN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SP helped in designing of the study and statistical analysis and formulating the final draft of the manuscript. Author DB is the co-author of the study and managed the analyses. Authors UB and RJ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Ovarian cancer is mostly diagnosed at an advanced stage due to its initial asymptomatic nature. It is often associated with high morbidity and mortality. Neo-adjuvant chemotherapy followed by interval debulking surgery is the primary modality of treatment accepted now a days. Our study was conducted in these cases and predictors of survival evaluated.
Aims: To study the clinicopathological factors predicting outcome survival in women with advanced ovarian cancer treated with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS).
Methods: A retrospective observational study was conducted over a period of two years from 1st January 2014 to 31st December 2015. All patients with serous epithelial ovarian tumors who received NACT (neo-adjuvant chemotherapy); 3 to 4 cycles followed by IDS (interval debulking surgery) followed by 3 cycles of adjuvant chemotherapy were studied. Factors influencing their overall survival were critically analyzed and evaluated.
Results: A retrospective study was conducted from 1st January 2014 to 31st December 2015; a total

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of 50 patients with carcinoma ovary were studied. All the patients belonged to stage III and above with a mean age of 46.16 years. All the patients had histopathology report of epithelial serous ovarian carcinoma and all the fifty patients received NACT followed by IDS and then adjuvant chemotherapy. At the end of 5 years, 24% patients were alive and 76% patients expired. The total recurrences in the study population was 86%. The mean overall survival at the end of 5 years was 15.2%. Absence of ascites post neo-adjuvant chemotherapy was a significant predictor of 5 year survival ($p<0.0001$). Type of resection, maximum tumor burden site and CA125 levels were also contributory prognostic factors in these patients.

Conclusion: The predictors of survival based on clinicopathological response to neoadjuvant chemotherapy after interval debulking surgery in advanced epithelial ovarian carcinoma include absence of ascites post NACT, R0 type of resection, maximum tumor burden at ovary or colon and post treatment mean CA125 levels of 33.97.

Keywords: Epithelial ovarian carcinoma; neo-adjuvant chemotherapy; interval debulking surgery; predictors of survival.

1. INTRODUCTION

In females, amongst gynaecological cancers ovarian cancer holds number three rank after cervix and uterine cancers [1]. Patients of ovarian cancer mostly present at an advanced stage and have a high mortality rate [2]. Since patients with carcinoma ovary belong to a higher stage at primary presentation; primary debulking surgery is often difficult and thus they have to be taken for neo-adjuvant chemotherapy initially followed by interval cytoreductive surgery. Percentage of patients with advanced ovarian cancer at presentation is around 75% and most of these cases often present with chemoresistance and extensive lesions of the peritoneum [3].

Vergote et al. [4] in their study concluded that primary chemotherapy in patients with advanced ovarian cancer offers a non inferior approach as compared to primary cytoreductive surgery for patients with stage IIIC or IV ovarian carcinoma.

Our study was conducted in patients with advanced ovarian cancer who primarily were given neo-adjuvant chemotherapy. Factors influencing survival were analyzed and followed up.

2. AIMS AND OBJECTIVES

To study the clinicopathological factors predicting outcome survival in women with advanced ovarian cancer treated with neoadjuvant chemotherapy (NACT) followed by Interval Debulking Surgery (IDS).

3. MATERIALS AND METHODS

- A retrospective observational study was conducted over a period of two years (1st January 2014 to 31st December 2015).
- All patients with serous epithelial ovarian tumors who received NACT (neo-adjuvant chemotherapy); 3 to 4 cycles followed by IDS (interval debulking surgery) followed by 3 cycles of adjuvant chemotherapy were studied.
- Factors influencing their overall survival were critically analyzed and evaluated.
- One year, three year and five year survivals were compared using univariate and multivariate analysis.
- The factors which were studied post NACT were: Ascites, location of maximum tumor burden, CA125 levels and type of resection.
- P value was calculated for all the factors separately and $p<0.05$ was considered significant.
- Recurrence of ovarian cancer was considered as per standard definitions as tumor recurrence after complete initial response to primary therapy, and a disease free interval of minimum six months.

4. RESULTS AND OBSERVATIONS

From 1st January 2014 to 31st December 2015, a total of 50 patients with carcinoma ovary were studied at Dr. B Borooah Cancer Institute, Guwahati, Assam. All the patients belonged to stage III and above with a mean age of 46.16 years with minimum age of 26 years and maximum age of 71 years. All the patients had

histopathology report of epithelial serous ovarian carcinoma and all the fifty patients received NACT followed by IDS and then adjuvant chemotherapy.

4.1 Outcome of Study Population

Out of the 50 patients, 12 (24%) patients were alive and 38 (76%) expired after 5 years follow-up. Amongst the 12 patients who were alive; 5 patients developed recurrence and 7 patients were disease free. Out of the thirty eight patients who expired; all of them developed recurrences. Thus, the total recurrences in the study population were 43that was 86% of the population.

4.2 Overall Survival (Diagram 1, Table1)

The mean overall survival at the end of 1 year, 3 years and 5 years was 86%, 25.6% and 15.2% respectively.

List 1. Post NACT outcomes

Post NACT Outcomes (after 5 years)		Alive=12	Dead=38
Ascites			
1.	Present	1	38
2.	Absent	11	0
CA125			
1.	>35	3	20
2.	<35	9	18
Type of resection			
1.	R0	12	26
2.	R1	0	10
3.	R2	0	2
Intra-operative maximum tumor burden			
		9	19
1.	Ovary	1	12
2.	Omentum	0	2
3.	Peritoneum	1	2
4.	Colonic	0	2
Deposit		1	1
5.	Mesentery		
6.	Nil (no disease seen)		

It was observed that women who died had ascites, increased CA 125 levels, underwent R1 or R2 type of resection and more commonly had extra-ovarian maximum tumor burden in the omentum, peritoneum, as a colonic deposit and in the mesentery.

All the above factors were then analyzed to predict the overall survival and level of significance calculated.

4.3 Predictors of Survival

1. **Ascites versus overall survival (Diagram 2, Table2):** After completion of 3 cycles of neo-adjuvant chemotherapy, the presence or absence of ascites was noted and the 1 year, 3 years and 5 years survival calculated and compared. It was seen that the 5 year survival rate in patients with absent ascites was 40.8% as compared to the patients with presence of ascites; whose survival rate was 0%. The p value was calculated as <0.0001 that was clinically significant. Thus, presence of ascites in our study population was a significant predictor of survival.
2. **Type of resection versus overall survival (Diagram 3, Table 3,4):** According to the cytoreductive scoring system; the type of resection was categorized as R0, R1 or R2. It was seen that when R0 resection was done, the 1 year, 3 year and 5 year survival rate was 86.8%, 34.8% and 28.5% respectively. For R1 type of resection; the 1 year, 3 year and 5 year survival rates were 90%, 20% and 0% respectively and for R2 type of resection the 1 year, 3 year and 5 years survival rates were 50%, 0%, 0% respectively. The hazard ratio was further calculated; keeping R0 resection as reference and the p value for the same was not significant. The hazard ratio (HR) for R1 resection was 1.645; p value=0.186 and for R2 resection was 3.076 with a p value=0.133.
3. **Maximum tumor burden versus overall survival (Diagram 4, Table 5):** Post NACT, when interval debulking surgery was done, the site of maximum tumor burden was noted and overall survival calculated for the same. The 5 year survival rate was 0% when the maximum tumor burden was present either in the mesentery or the peritoneum. 50% five year survival rate was seen when complete response was present after NACT. When the maximum tumor burden was present in ovary, the 5

year overall survival rate was 27.4% and it was 33.3% when the maximum tumor burden was present as a colonic deposit. The p value for maximum tumor burden versus overall survival was 0.328 that was not significant.

4. **CA125 levels post treatment versus survival:** The Ca125 levels were seen post treatment that is NACT followed by IDS followed by adjuvant chemotherapy. It was seen that mean CA125 levels in patients who were alive post treatment was 33.97 as compared to 72.98 in patients who were dead. Also, the median CA125 levels were 9.9 and 30.8 in alive and dead patients respectively. The survival was seen post five years.

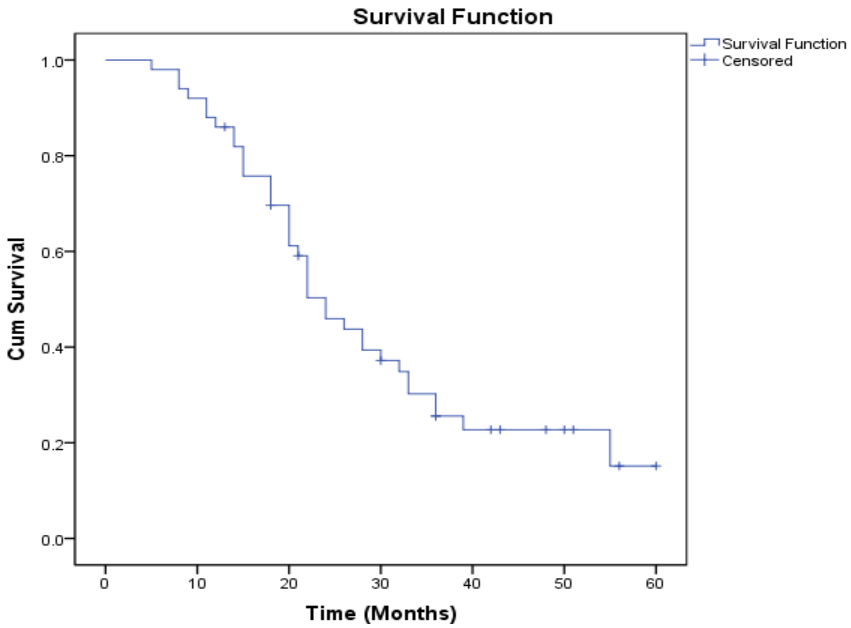

Diagram 1. Overall survival

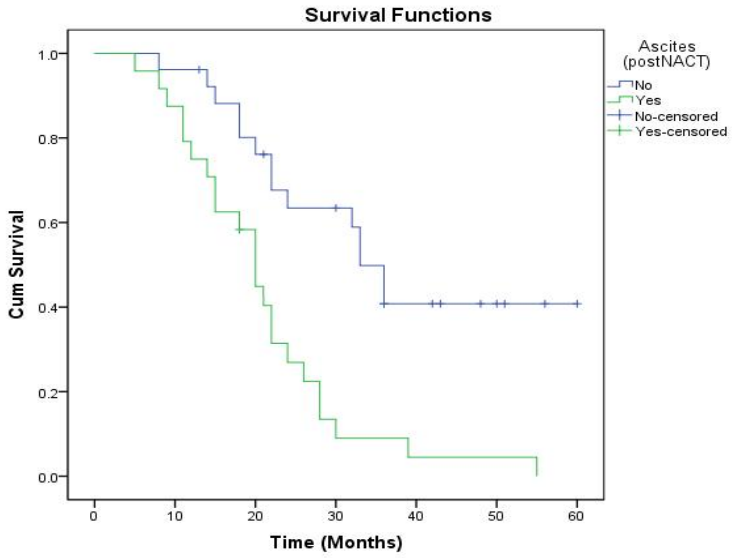

Diagram 2. Ascites versus overall survival

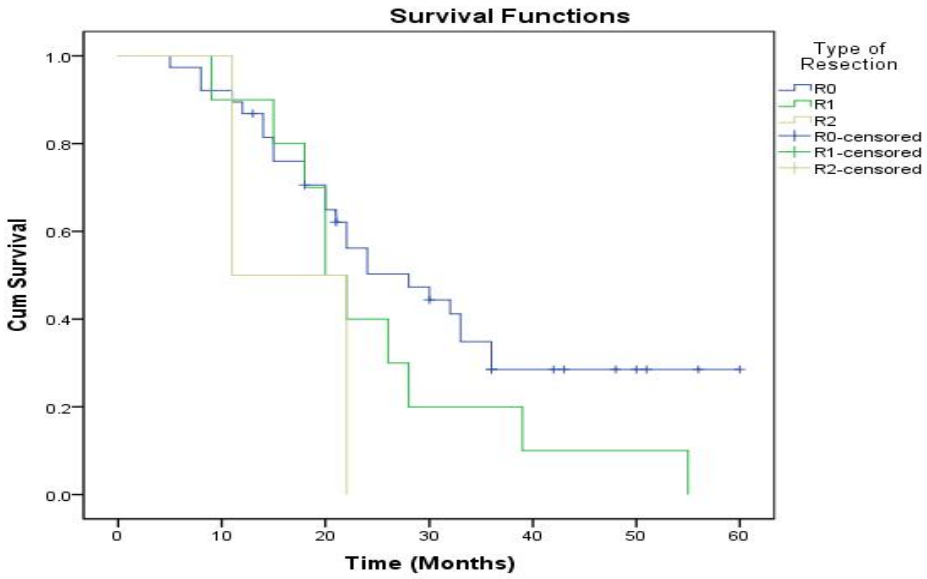

Diagram 3. Type of resection versus overall survival

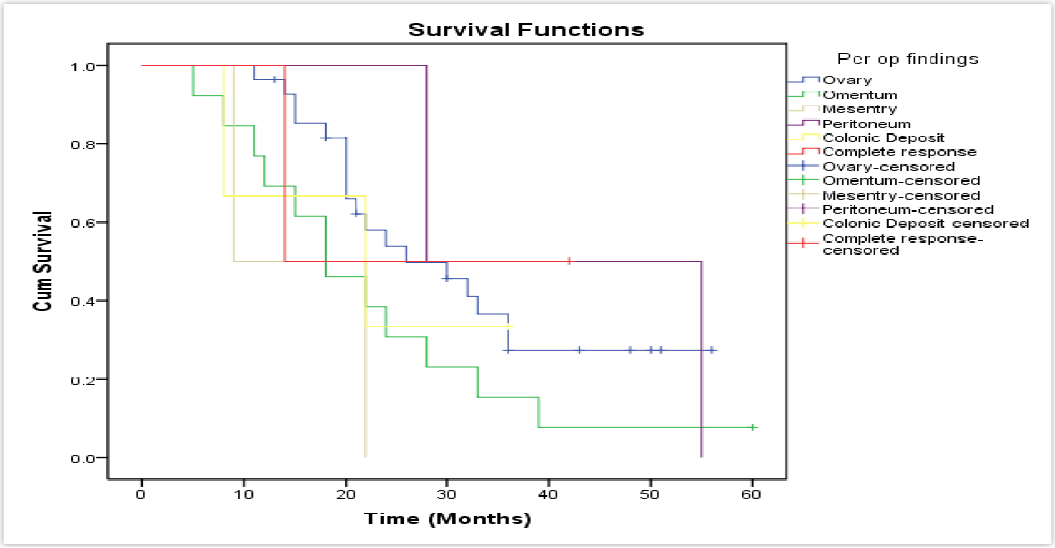

Diagram 4. Maximum tumor burden versus overall survival

Table 1. Overall Survival

Overall Survival	1 Year	3 Year	5 year
Mean	86%	25.6%	15.2%

Table 2. Ascites versus overall survival

Ascites (post NACT)	1 year OS	3 year OS	5 year OS
Absent	96.2%	40.8%	40.8%
Present	75%	9%	0%

Table 3. Type of resection versus overall survival

Type of Resection	1 year OS	3 year OS	5 year OS
R0	86.8%	34.8%	28.5%
R1	90%	20%	0%
R2	50%	0%	0%

Table 4. Type of resection; Hazard ratio

Type of Resection	Hazard Ratio	P value
R0	Ref	-
R1	1.645	o.186
R2	3.076	0.133

Table 5. Maximum tumor burden versus overall survival

Max Tumor Burden	1 year OS	3 year OS	5 year OS
Ovary	96.4%	36.5%	27.4%
Omentum	69.2%	15.4%	7.7%
Mesentry	50%	0%	0%
Peritoneum	50%	0%	0%
Colonic deposit	66.7%	33.33%	33.3%
Complete Response	50%	50%	50%

5. DISCUSSION

In our study, we retrospectively analyzed 50 patients from January 2014 to 31st December 2015 of advanced stage carcinoma ovary and studied the predictors of survival based on clinic-pathological response post neo-adjuvant chemotherapy. It was seen that absence of ascites, R0 or R1 resection, lower CA125 levels post treatment and maximum tumor burden either in ovary or colon are good predictors of survival. But, absence of ascites was the only significant predictor in these patients when compared with 5 year overall survival. Our study population belonged to North-eastern part of India.

A similar study was conducted by Marco Petrillo et al. [5] with the objective to analyze the role of pathological response as a prognostic factor in patients with unresectable advanced ovarian cancer post neoadjuvant chemotherapy. They divided their patients based on the pathological response seen on NACT. They had 3 categories which were cPR that is complete, microPR that is < or =3mm residual disease or macroPR. They concluded that in cases with advanced ovarian cancer, the likelihood to achieve complete pathological response was uncommon and thus justifying the importance of NACT.

Miho Muraji et al. [6] also conducted a retrospective study from 2001 to 2010 on 124 patients with epithelial ovarian cancer who were given NACT initially and then taken up for IDS and then finally were given adjuvant chemotherapy. The median age for their group of patients was 62 years whereas the mean age of our study population was 46.16 years. They concluded that in their study more than 1 cm of residual disease, higher stage of cancer and active disease on histopathology of excised specimen during surgery are independent factors to predict overall survival.

Ce Bian et al. [7] published their paper in 2016 comparing NACT followed by IDS and primary debulking surgery in patients with ovarian cancer. They found out that there was no survival benefit when the two protocols were compared but they also concluded that in the NACT group, residual tumor, age and FIGO stage were statistically significant independent predictors of overall survival.

Yan Gao et al. [8] evaluated 220 patients of advanced ovarian carcinoma retrospectively. They studied the benefits of NACT in these cases. They found out that there was no difference in progression free survival and overall survival in the NACT versus Primary Debulking Surgery (PDS) group. They concluded that chemosensitivity was more in patients with no residual disease that is R0 resection in both NACT and PDS groups and thus improved their survival. Their results were comparable to our study that also showed better survival rates in patient who underwent a R0 resection.

The ROVAR score or the risk of ovarian cancer relapse score was proposed in a recent study as one of the important prognostic factors in predicting relapse in patients with advanced ovarian cancer after primary treatment [9]. The factors that were included in their scoring system were CA125 levels, FIGO stage and grade of ovarian cancer, post treatment commuted tomography scan and residual disease. In our study also, post treatment CA125 levels and type of resection influenced survival of the study population.

Son JH et al [10] conducted a study for prediction of suboptimal debulking surgery in patients with advanced ovarian carcinoma post NACT. They evaluated a total of 68 patients and concluded that reduced levels of CA125 levels after second cycle of NACT, low BMI and small bowel mesentery involvement on commuted tomography are good predictors of residual disease on interval debulking surgery post NACT. In our study also it was seen that when the maximum tumor burden was found in the mesentery, the 5 year survival rate was 0%.

CA125 levels as a predictor of optimal interval debulking surgery post NACT was also studied by Jing Zeng et al. [11]. They evaluated a total of 118 patients belonging to FIGO stage III and IV epithelial ovarian cancer. Their results also concluded that CA125 levels of less than 200 post neo-adjuvant chemotherapy is a good predictor to obtain no visible residual disease on interval debulking surgery and hence improved chemosensitivity.

The role of histological features as predictors of survival for patients with advanced stage ovarian cancers treated with NACT was evaluated by Samrao D et al. [12]. 67 patients were evaluated in their study and features like fibrosis, necrosis, residual tumor and inflammation were evaluated. They found out that fibrosis and necrosis were poor prognostic factors in their study population and led to shorter recurrent free survival outcomes.

6. CONCLUSION

In women with advanced ovarian cancer; NACT could be beneficial in decreasing the tumor burden thereby facilitating complete surgical debulking and overall survival of patient.

Factors like CA125 levels, ascites (post NACT), maximum tumor burden, type of surgical resection significantly affects the overall survival of these patients.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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