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RESEARCH PAPER

A Predictive Score after Neoadjuvant Chemotherapy for Optimal Cytoreduction at Interval Debulking Surgery in Advanced Epithelial Ovarian Cancer

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Abstract

Background: Ovarian cancer is the seventh most common cancer and eighth most common cause of death of female. More than 75% patients are diagnosed at Stage (III - IV) and their 5-year survival rate is (25-50%) . Primary debulking surgery (PDS) followed by adjuvant chemotherapy is the cornerstone treatment for advanced ovarian cancer. Unfortunately, primary debulking surgery is not always feasible and not associated with optimal cytoreduction. Recently, neoadjuvant chemotherapy followed by Interval Debulking Surgery (NACT- IDS) is increasingly adopted. (NACT-IDS) improves optimal cytoreduction and reduces complications in comparison with PDS . However, a significant proportion of patients cannot be optimally cytoreduced even after NACT-IDS and causes futile laparotomy. So, it is necessary to develop a Predictive Score for Cytoreduction (PSC) after NACT for optimal cytoreduction at (IDS).

Objective: To find out a predictive score after NACT for optimal cytoreduction at IDS in advanced epithelial ovarian cancer.

Method: This was a prospective observational study conducted among 55 patients of advanced ovarian cancer to develop a predictive score after NACT at IDS in department of Gynecological Oncology of BSMMU, from January 2020 to December 2020.

Result: Among the 55 patients with advanced epithelial ovarian cancer 44(80%) could be optimally cytoreduced whereas in 11(20%) suboptimal cytoreduction occurred. The sensitivity, specificity, Negative predictive value (NPV), Positive predictive value (PPV) and accuracy of CA-125 for prediction of optimal cytoreduction was 87.5%, 30.8%,85.7%,34.1% and 47.3% respectively. It was observed that 37 (84.1%) have peritoneal cancer index within 0-16 in optimal cytoreduction (R0) and 3 (27.3%) in non-R0 (*p value* 0.001). The sensitivity, specificity, NPV, PPV and accuracy of Peritoneal Cancer Index (PCI) for prediction of optimal cytoreduction was 62.5%, 89.7%, 85.4% 74.1% and 81.8% respectively. PSC after NACT for optimal cytoreduction at (IDS) was 3 and it indicates 83.3% Patients could be optimally cytoreduced limiting the rate of suboptimal cytoreduction in 16.7%.

Conclusion: The result of the present study showed that PSC after NACT influences Optimal cytoreduction (R <1cm) at (IDS). So, this study concluded that IDS after NACT should be performed in patients with a PSC up to 2 to avoid suboptimal cytoreduction.

Keywords: Neoadjuvant chemotherapy, Advanced Epithelial ovarian cancer (EOC), optimal cytoreduction (R0) suboptimal cytoreduction (non-R0), Predictive Score for Cytoreduction (PSC), Peritoneal Cancer Index (PCI)

Introduction:

Ovarian cancer is the seventh most common cancer and eighth most common cause of death from cancer in women, overall. There are nearly 3,00000 new cases detected and 184,799 deaths occurred due to ovarian cancer in 2018.[1] Ovarian cancer accounts for 2.5% of all female cancer and 5% of cancer death because the disease is of low survival.[1] The management of advanced ovarian cancer requires multimodality therapy to achieve the most successful outcome, ideally by primary optimal cytoreductive surgery followed by adjuvant chemotherapy. This management protocol has been considered as the only standard treatment for advanced epithelial ovarian cancer (EOC).[2] However some women may not be appropriate candidate for primary debulking surgery (PDS) because of associated medical conditions, like

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congestive heart failure, recent myocardial infarction or unresectable tumor,(clinically hard fixed irregular mass) presence of huge ascites, Pouch Douglas nodule pleural effusion and radiographic findings of omental metastasis and peritoneal metastasis. In these patient's upfront use of 3-4 cycles of platinum based neoadjuvant chemotherapy followed by Interval Debulking Surgery (IDS) is a better option.[3]

Interval Debulking Surgery (IDS) was first introduced in 1995 by European Organization for the Research and Treatment of Cancer (EORTC). Optimal cytoreduction means macroscopic residual tumor less than < 1 cm which is the best survival predictor in advanced Epithelial Ovarian Cancer [EOC]. The optimal debulking rate is 16% in PDS group compared to 40% in NACT – IDS group and the median overall survival (OS) was only 30 months in PDS which is considerably less than NACT – IDS (60+ months).[4] Postoperative death [death within 28 days after surgery] occurred in 2.5% patients in the PDS group and 0.7% of patients in the NACT – IDS group. Infection 8.1% and 1.7% respectively and venous thrombosis complications is 2.6% and 0% respectively.[5] But, a significant portion of patients cannot be optimally cytoreduced even after NACT-IDS and this increases the morbidity and mortality of the patients with no expected survival benefit.

So, a key issue in patients with advanced epithelial ovarian cancer (EOC) is the selection of patients suitable for optimal cytoreduction after NACT at Interval Debulking surgery.

A predictive score after NACT for optimal cytoreduction at Interval Debulking Surgery (IDS) is made based on CA-125, and peritoneal cancer index (PCI) by CT scan.

Laparoscopy has also been proposed as predictor for optimal cytoreduction in NACT– IDS which reduces the rate of suboptimal cytoreduction (Futile laparotomies).But in ovarian cancer patient's laparotomy is considered better than laparoscopy. In laparotomy inspection and palpation of organ is possible which is important for surgical staging of ovarian cancer. Laparoscopy cannot provide such information. Moreover, there is a risk of intraperitoneal tumor rupture and trocar metastasis.[5] In addition, anatomical and technical limitations make the exploration difficult in some areas (diaphragmatic dorsal area, mesenteric retractions).[6]Therefore, it is important to develop a predictive score after NACT which is indicative of successful optimal cytoreduction at interval debulking surgery (IDS). This will decrease morbidity, infection, postoperative death and vascular complications and above all decrease unnecessary laparotomies. The objective of this study is to develop a preoperative predictive score following NACT which will reflect surgical outcome at IDS in advanced epithelial ovarian cancer. This will enable to select patients of advanced epithelial ovarian cancer who will be maximally benefited with surgery at Interval Debulking surgery.

Materials and method

This prospective observational study was conducted in gynecological oncology department of Bangabandhu Sheikh Mujib Medical University over a period of 12 months from January 2020 to December 2020. A total of 55 patients with confirmed histopathological diagnosis (core biopsy) of advanced epithelial ovarian cancer (III – IV) who received 3-4 cycles of platinum-based chemotherapy followed by Interval Debulking Surgery (IDS)were included in this study.

The purpose and procedure of the study was discussed and informed written consent was taken from the patients. Ethical committee clearance was obtained from IRB of BSMMU. Information was collected through a pre-designed questionnaire. All patients were subjected to NACT and serum CA-125 before NACT were measured. CT scan of whole abdomen and pelvis after NACT was also done. Firstly, Univariate analysis of variables -age, ECOG performance status of patient, histology, staging and grading of tumor, CA 125, PCI (by CT scan) associated with optimal cytoreduction at IDS was done. Then a PSC was obtained by calculating sensitivity specificity, (NPV), (PPV) and accuracy of significant variables CA-125 and Peritoneal Cancer Index (Age, ECOG-PS, histology, staging and grading of tumor were not included in scoring system.)Accuracy of >75% were scored as 2 and<75% as 1.Predictive Score >3 was considered not suitable for optimal cytoreduction (non-R0) and ≤3 considered suitable for optimal cytoreduction (R0).Statistical analysis of the results was obtained by using window-based computer software device with Statistical Packages for Social sciences (SPSS-22).

For continuous variables unpaired t– test and for qualitative variables Chi-square test was done to see

the significance of difference between two groups. Performance of diagnostic tests was assessed by calculating sensitivity, specificity. Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy. To determine cutoff point of quantitative variable (CA 125) ROC curve was used. P value <0,05 was considered as statistically significant.

Results

Among 55 patients 44 (80%) patients could be optimally cytoreduced and labeled as group I (R0) and 11(20%) patients could not be optimally cytoreduced means suboptimal cytoreduction occurred labeled as group II (non-R0). It was observed that 12(27.3%) patients belong to 40-50 years in R0 group whereas only 1 (9.1%) patient in non R0 group (p value 0.001). The mean age was 45.95 ± 13.11 years in optimal cytoreduction (R0) and 64.09 ± 7.5 years in suboptimal cytoreduction (non-R0) group. On the basis of stage of disease 31(70.5%) patients were in stage IIIa in R0 and 3 (27.3%)patients in non-R0 (p value 0.022). It was observed that more than half 26 (59.1%) patients had serous cystadenocarcinoma in R0 and 5(45.5%) patients in non-R0. The differences was statistically not significant (*p value*0.715) between two groups. It was observed that based on grading more than half 23 (52.3%) patients had grade-I tumor in R0 and 3(27.2%) patients in non-R0. The differences were statistically not significant (*p* value 0.269) between two groups. Which table shows the profile of the study patients by ECOG performance status. It was observed that almost three fourth 32 (72.7%) patients had restricted strenuous activity in R0 and 4(36.4%) in non-R0. The differences were statistically significant (*p value* 0.023) between two groups.

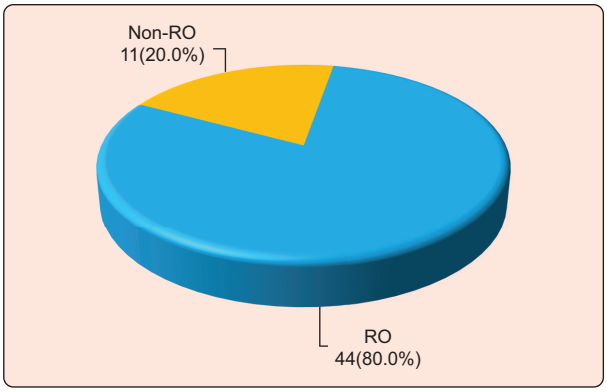

Figure 1: Pie-chart showing distribution of the study patients by R0 status

Table I: Profile of the study patients by stage of tumor (n=55)

Stage of tumor	R0 (n=44)		Non-R0 (n=11)		P value
	n	%	n	%	P value
III	31	70.5	3	27.3	0.022[s]
IIIa	2	4.5	2	18.2	
IIIb	3	6.8	0	0.0	
IIIc	1	2.3	0	0.0	
IV	7	15.9	6	54.5	

s= significant
p value reached from Chi-square test

Table I shows the profile of the study patients by stage of tumor. It was observed that more than two third (70.5%) patients had stage III in R0 and 3(27.3%) in non-R0. The difference was statistically significant (p<0.05) between two groups.

Table II: Profile of the study patients by peritoneal cancer index (n=55)

Peritoneal Cancer Index	R0 (n=44)		Non-R0 (n=11)		P value
	n	%	n	%	
0-16	37	84.1	3	27.3	0.001[s]
>16	7	15.9	8	72.7	

s= significant
p value reached from Chi-square test

Table II shows the profile of the study patients by peritoneal cancer index. It was observed that among R0 group (44) 84.1% (37) patients were within 0-16 (PCI) and among non-R0 group (11) 27.3% (3) patients were within 0-16 (PCI). The difference was statistically significant (p<0.05) between two groups.

Table III shows the mean preoperative CA-125 level was 786.8±249.4u/ml in R0 and 1123.2± 549.03 u/ml in non-R0 (p value 0,004). Receiver Operator Characteristic (ROC) curve was used to determine the cut off value of CA -125 which was 685u/ml. The area under curve (AUC) is 0.696 confidence Interval was 0.522-0.871. The sensitivity, specificity, NPV, PPV and accuracy of CA-125 for prediction of optimal cytoreduction was 87.5%, 30.8%,85.7%,34.1% respectively

Table III: Receiver-operator characteristic (ROC) curve of CA-125 for prediction of optimal cytoreduction in advanced epithelial ovarian cancer.

	Cut off value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
CA-125	685.0	87.5	30.8	0.696	0.046	0.522	0.871

Table IV: Diagnostic performance and Predictive Score for cytoreduction (PSC)

Variable	Sens (%)	Spec (%)	NPV (%)	PPV (%)	ACC (%)	PSC score
CA-125	87.5	30.8	85.7	34.1	47.3	1
PCI >16	62.5	89.7	85.4	71.4	81.8	2

Table V: Performance of predictive score at Interval Debulking Surgery (IDS)

Variable	Optimal NPV (%)	Cytoreduction	Futile laparotomies (1-NPV) (%)
PSC -3	83.3		16.7

Table IV shows the validity of serum CA-125 level and PCI for evaluation of advanced epithelial ovarian cancer was correlated by calculating sensitivity, specificity, Negative predictive value (NPV) and Positive Predictive Value (PPV) and accuracy. A predictive score after NACT for optimal cytoreduction (PSC) was made based on accuracy. Accuracy of serum CA-125 was <75% and 1 point was assigned, accuracy of PCI by CT scan was >75% and 2 points were assigned. So, the score of PSC was three (3). Age. ECOG performance status, histological type, staging and grading of tumor were not included in scoring system.

Table IV: shows the level of optimal and suboptimal cytoreduction on the basis of PSC score. It was observed that 83.3% patients could be optimally cytoreduced whereas only 16.7% patients could not be optimally cytoreduced (suboptimal cytoreduction) in PSC score three (3).

It was observed that majority 37 (84.1%) patients have peritoneal cancer index within 0-16 in R0 and 3(27.3%) in non-R0 (*p value* 0.001). The sensitivity, specificity, NPV, PPV and accuracy of PCI for prediction of optimal cytoreduction was 62.5%, 89.7%, 85.4% 74.1% and 81.8% respectively. Preoperative predictive score was made based on accuracy of CA-125 and Peritoneal Cancer Index(PCI). Age, ECOG-PS, staging, grading and histological type of tumor were not included in scoring system. Preoperative predictive score after NACT for optimal cytoreduction at interval debulking surgery (IDS) was3 and it indicates 83.3% Patients could be optimally cytoreduced limiting the rate of suboptimal cytoreduction in 16.7% patients in advanced epithelial ovarian cancer

Discussion:

The 5 years survival of advanced epithelial ovarian cancer is about (30-50%) in most countries.[7] It is estimated that in 2020 year 21,750 new cases of ovarian cancer were diagnosed & 13,940 women died in USA.[8]

In this current study, it was observed that almost one forth 12 (27.3%) patients belonged to age 41-50 years in R0 and 1 (9.1%) patient in non-R0 group. The mean age was 45.95 ±13.11 years in R0 and 64.09 ± 7.75 in non R0. The difference was statistically significant (p<0.05).in term of age.

In this present study it was observed that the mean CA-125 before NACT was 786. ±249.4 in R0 and 1123.2 ± 549.03 in non-R0. The difference was statistically significant (p value < 0.05). All patients were given neoadjuvant chemotherapy (NACT) and after neoadjuvant chemotherapy (NACT) Interval Debulking Surgery was done. Out of 55, 47 (85.7%) patients underwent optimal cytoreduction. Sonia Batra

et al. 2020 had shown in her study that out of 50, 35 (77.8%) patients were underwent optimal cytoreduction on the basis of CA-125 level which is consistent with the present study.[9]

Here, it was observed that among R0 group (44) 84.1% (37) patients were within 0-16 (PCI) and among non-R0 group (11) 27.3% (3) patients were within 0-16 (PCI). The difference was statistically significant in two groups ($p<0.05$). The specificity of peritoneal cancer index by CT scan to identify patients undergoing optimal debulking was 89.7%. Young Jong Song 2020 also showed the specificity of CT scan to identify patients undergoing optimal cytoreduction was 85% which is consistent with the current study.[10]

Young Jong Song also showed the sensitivity, specificity and negative predictive value of predictive index score (PIS) for prediction of optimal cytoreduction was 100%, 85% and 87.5% respectively.[10] In this present study the sensitivity, specificity and negative predictive value of Predictive Score of Cytoreduction (PSC) for prediction of optimal cytoreduction were 95.45%, 90.9% and 83.3% respectively which is consistent with the previous study.

In the present study it was observed that at multivariate analysis only CA125 ($p=0.004$) and PC I($p=0.001$) maintained the statistical significance. Peritoneal Cancer Index (PCI) had the accuracy >81.8%. Preoperative predictive score after NACT was three (3) at IDS had indicated that optimal cytoreduction could be done in (83.3%) patients by limiting suboptimal cytoreduction in (16.7%) patients. Eleona Ghisoni et al. also showed the accuracy of PCI was 82.3% and PSC > 3 had indicated 83.5% complete cytoreduction could be done limiting the suboptimal cytoreduction at 16.5% which is consistent with this study.[5]

Philipp Harter et al showed in their study the rate of complete resection was 76%, thus confirming the validity of this score regarding positive prediction of complete respectability in 2 out of 3 patients.[11] In the present study it was observed that the rate of complete resection was 80% and this confirm the validity of score regarding positive prediction of complete respectability which is consistent with this previous study.

Conclusion

The result of the present study, showed that preoperative predictive score after NACT influences Optimal cytoreduction (R <1cm) at Interval Debulking Surgery (IDS) In this study predictive score (PSC) after NACT for optimal cytoreduction at IDS was three (3) and in this score 83.3% patients could be optimally cytoreduced limiting the rate of suboptimal cytoreduction in 16.7% patients. So, this study concluded that IDS after NACT should not be performed in patients with a PSC up to 3 to avoid suboptimal cytoreduction.

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