Primary Cytoreductive Surgery versus Neoadjuvant Chemotherapy followed by Interval Cytoreductive Surgery for Advanced Epithelial Ovarian Cancer: A Retrospective Cohort Study

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Abstract

Introduction: Epithelial ovarian cancer (EOC) represents about two-thirds of ovarian malignancies and usually presents with advanced disease. Primary cytoreductive (PCR) surgery is known to be the cornerstone of treatment of advanced EOC, but it might not always be feasible to obtain optimal cytoreduction. Neoadjuvant chemotherapy (NACT) has been proposed as an alternative approach. This study aims to compare the survival of patients, post-operative morbidity and the extent of cytoreduction that was achieved among the two treatment groups. **Methods:** A retrospective cohort study was done in Bhaktapur Cancer Hospital of Nepal. All women who underwent surgical management for advanced epithelial ovarian cancer from 2016 to 2019 were included in the study and analyzed using SPSS version 23. **Results:** Among 29 cases of advanced EOC, seven cases underwent PCR and 22 cases had NACT followed by interval cytoreduction (ICR). Optimal debulking was achieved in 85.7% of the cases in the PCR group and in 95.5% in the NACT+ICR group. Overall survival of >3 years in the PCR group was 42.9% while in the NACT group was 59.1%. Progression free survival (PFS) of >3 years was seen in 28.6% in the PCR group and in 45.5% in the NACT group. **Conclusions**: The current study shows that NACT followed by ICR has better survival outcomes than PCR. Despite the limitations of the study, NACT + ICR can be considered a reasonable alternative to PCR in advanced EOC.

Keywords: epithelial ovarian cancer; morbidity; neoadjuvant therapy; survival.

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Introduction

Ovarian cancer is the second most common gynaecologic cancer in the world with a high fatality to case ratio. Its incidence in Nepal is 3.88%.[12]Among ovarian cancers, epithelial ovarian cancer (EOC) is the mostcommon and about 2/3rd of them present with advanced disease due to vague symptoms and lack of effective screening programmes..[3]

Primary cytoreductive surgery (PCR) followed by adjuvant chemotherapy is said to be the treatment of choice for advanced EOCs However, optimal debulking might not always be possible at the time of diagnosis. Moreover, in patients who are medically unfit, aggressive debulking might not be an option. In such cases neoadjuvant chemotherapy (NACT) followed by interval cytoreductive (ICR) surgery and post-operative chemotherapy has been proposed as an alternative approach.[4]

This study aims to compare the survival of patients, post-operative morbidity as well as the extent of cytoreduction among the two treatment groups.

Methodology

A retrospective cohortstudy was done in Bhaktapur Cancer Hospital of Nepal. Data collection was done from February 2022 to July 2022 from the patient's record file after ethical approval from the Institutional Review Board. All women who underwent surgical management for advanced epithelial ovarian cancer from 2016 to 2019 were included in the study. Patients with other significant comorbidities like COPD, heart disease, chronic kidney disease, uncontrolled diabetes, history of stroke, other concurrent malignancy, patients aged >75 years, those who have defaulted or with missing data, those treated with palliative intent or those who underwent cytoreductive surgery elsewhere were excluded.

The name and hospital encounter ID of the patients who had undergone surgery for epithelial ovarian cancer were first obtained from the entry register of the operation theatre after which the patient's hospital record file were extracted from the record section. Detailed history including age, parity, demographic profile, menopausal status etc.was obtained. Details on physical examination and imaging reports were obtained to determine the stage of the cancer. Data on preoperative workup including tumor markers were obtained. Performance status of the patient prior to treatment and postoperative morbidity (complications, duration of hospital stay) were determined. Progression free survival (PFS) and overall survival were determined by tracing their follow up reports. In addition to this, the histopathological findings were also noted.

Data was primarily entered in an individual form and analysis was made usingStatistical Package for the Social Sciences (SPSS) version 23 and was depicted in the form of tables.

Results

During the study period, a total of 29 cases of advanced epithelial cancer were taken, of

which 22 cases underwent NACT followed by ICR and 7 cases underwent PCR.

Table 1: Age-wise distribution of two groups (n=29)

	PCR			NACT + ICR			p-value
	Median	Q1	Q3	Median	Q1	Q3	
Age	54	32	60	62	48	65.25	0.12

The age of the patients that were included in the study ranged from 29 to 75 years with a mean age of 55.8 years. In the PCR group the median age was 54 while in the ICR group the median age was 62(Table 1).

Table 2: WHO performance status of patients (n=29)

WHO performance status	PCR (%)	NACT + ICR (%)	p-value
0	4 (57.1)	16 (72.7)	0.759
1	3 (42.9)	6 (27.3)	

The WHO performance status of all the included patients was either zero or one. Out of total participants, 57.1%(4/7) of patients in the PCR group and 72.7% (16/22) in the ICR group had WHO performance status zero, while 42.9% (3/7) in the PCR group and 27.3% (6/22) in the ICR group had performance status of one.

Among PCR group, 28.6% were FIGO Stage IIIA, 14.3% in Stage IIIB and 57.1% in Stage IIIC while in the NACT+ICR group, 77.3% were in Stage IIIC, 4.5% in Stage IVA and 18.2% in Stage IVB. So, patients with FIGO Stage IIIB and above whose disease seemed unresectable were subjected to NACT followed by ICR. 28.6% of patients in the PCR group were hypertensive. In the NACT+ICR group, 4.5% were diabetic, 9.1% were hypertensive and another 4.5% had both HTN and Diabetes.

Table 3: FIGO stages of patients (n=29)

FIGO Stage	PCR (%)	NACT + ICR (%)	p-value
Stage III A	2 (28.6)	0	0.031
Stage IIIB	1 (14.3)	0	
Stage III C	4 (57.1)	17 (77.3)	
Stage IVA	0	1 (4.5)	
Stage IV B	0	4 (18.2)	

Table 4: Comorbidities in patients (n=29)

Comorbidities	PCR (%)	NACT + ICR (%)	p-value
None	5 (71.4)	18 (81.8)	0.584
DM	0	1 (4.5)	
HTN	2 (28.6)	2 (9.1)	
HTN and DM	0	1 (4.5)	

The CA-125 levels among patients prior to treatmentranged from 243 to 5000, while the CEA levels ranged from 0.4 to 106.5. The median CA-125 levels in the PCR group were 635.6 and 802.5 in the NACT+ICR group. The median CEA level was 1.5 in PCR group and 1.135 in the NACT+ICR group. The Man Whitney U test did not show any significant difference between the CA-125 (p=0.475) and CEA (p=0.241) levels between the two groups.

The complexity of surgery was determined by the amount of blood loss, the duration of surgery, the presence or absence of adhesion, the degree of bowel or bladder injury during

surgery and the requirement of extra organ resection.

Table 5: CA-125 and CEA levels among patients

	PCR	NACT + ICR	p-value	
	Median	Median		
CA125	635.6	802.35	0.475	
CEA	1.5	1.955	0.241	
	Minimum	Maximum	Mean	Standard Deviation
CA125	243	5000	928.0	846.4
CEA	0.4	106.5	5.8	19.4

Table 6: Comparison of Complexity of Surgery (n=29)

Complexity of surgery	PCR (%)	NACT + ICR (%)	p-value
Low	0	5 (22.7)	0.424
Intermediate	7 (100)	15 (68.2)	
High	0	2 (9.1)	

Based on these findings 100% of the cases had intermediate level of complexity during primary cytoreductive surgery, while in the NACT+ ICR group, 22.7% had low levels of complexity, 68.2% had intermediate levels of complexity and 9.1% had high level of complexity. However the difference between the two groups were not statistically significant (p=0.424).

Table 7: Post operative complications (n=29)

Postoperativecomplication	PCR (%)	NACT + ICR (%)	p-value
Yes	0	2 (9.1)	1
No	7 (100)	20 (90.9)	

There were no post operative complications in the PCR group, while in the NACT+ ICR group, there were two cases of post operative complication which were wound dehiscence and fecal leakage for which colostomy bag was kept.

Table 8: Residual disease (n=29)

Residualdisease	PCR (%)	NACT + ICR (%)	p
CC0	6 (85.7)	21 (95.5)	0.976
CC1	1 (14.3)	1 (4.5)	

In the PCR group optimal debulking was achieved in 85.7% of the cases, while in the NACT + ICR group 95.5% of the patients had optimal debulking. However this difference in the two groups was not statistically significant (p=0.976).

In the PCR group, 57.1% had an overall survival (OS) of 1-3 years and 42.9% had an OS of >3 years. Similarly, 14.3% had a Progression free Survival (PFS) of <1 year, 57.1% had a PFS of 1-3 years and 28.6% had a PFS of >3 years. In the ICR group, OS of < 1 year was seen in 18.2%, 1-3 years in 22.7% and >3 years in 59.1%. Similarly PFS of <1 year was seen in 27.3%, 1-3 years in 27.3% and >3 years in 45.5%. Thus, there was no significant difference in the overall survival

and the progression free survival among the two groups (p=0.225 and 0.409 respectively).

Table 9: Overall Survival and Progression free Survival (n=29)

Overall Survival	PCR (%)	NACT + ICR (%)	p
<1year	0	4 (18.2)	
1-3years	4 (57.1)	5 (22.7)	
>3years	3 (42.9)	13 (59.1)	0.225
Progression free Survival	PCR	NACT + ICR (%)	p
<1year	1	6 (27.3)	0.409
1-3years	4	6 (27.3)	
>3years	2	10 (45.5)	

Discussion

The main aim of subjecting patients with advanced epithelial ovarian tumor to primary cytoreductive surgery or to NACT followed by interval cytoreductive surgery is to reduce the intraabdominal tumor burden which in turn enhances the survival outcome of patients[6]**.**The presence of residual disease after surgery is one of the most adverse prognostic factors for survival**.** Therefore, every attempt should be made to surgically resect as much disease as safely possible[4]**.**All patients received platinum-based chemotherapy. The median number of neoadjuvant chemotherapy cycles was three (range of 3-6). The duration between the last cycle of NACT and interval debulking was 4-6 weeks. Adjuvant chemotherapy was started about four weeks after primary or interval debulking.

In the present study comparison between the two modalities of treatment was done by the complexity of the surgery, the postoperative complications, the amount of residual disease and the overall and progression free survival of the patients. Among the study group, only 10.34% of the patients were Stage IIIA and IIIB while the remaining were Stage IIIC and higher. All patients in the NACT group were Stage IIIC and higher. This could be a reason for increased complexity of surgery in this group.

The postoperative complications and the duration of hospital stay were similar in both the groups with median hospital stay of 7-8 days. The proportion of patients who had no residual disease (CC0) was 85.7% in PCR group and 95.5% in the NACT group. This finding was comparable to a retrospective study done by M. Hegazy et al.[4] which showed a higher rate of optimal cytoreduction (72.2%) in the NACT group than in the PCR group (62.4%).The strongest independent predictor of prolonged survival in ovarian cancer is the absence of residual tumor after surgery. In a meta-analysis by Chang among patients with stage IIB or higher EOC who underwent cytoreduction and platinum/ taxanes chemotherapy, each 10% increase in the proportion of patients undergoing complete cytoreduction to no gross residual disease was associated with a 2.3-month increase in median survival compared with a 1.8-month increase for optimal cytoreduction.[7]

The overall survival of >3 years in the PCR group was 42.9% while in the NACT group was 59.1%. The survival percentage in the present study is greater in the NACT group than in the PCR group as compared to the CHORUS trial[8] (3 years survival of 32%

in PCR and 34% in NACT) and the EORTC trial[5] (median survival of 29 months in PCR group and 30 months in NACT).Similarly, the progression free survival (PFS) of >3 years was seen in 28.6% in the PCR group and in 45.5% in the NACT group. The overall survival and the progression free survival were both better in the NACT group as opposed to a retrospective study done by Rauh-Hain et al.[9], which showed improved survival outcome in the PCR group compared to NACT. Another retrospective study by Dabi et. al. using maintained databases from seven French referral gynecologic oncology institutions concluded that patients treated with up front surgery had longer progression free and overall survival than those treated with NACT–IDS ($p < 0.001$ and $p = 0.03$,respectively).[10]In a prospective study done in Netherlands, progression within 6 months after last chemotherapy cycle in patients who underwent PCR was seen in 32% while progression was seen in 40% in those patients who underwent ICR. The progression free survival and disease specific survival was also greater for patients who had PCR (17 months and 40 months respectively) as compared to those who had ICR (14 and 33 months respectively).[11]However, in a Cochrane review that included three randomized controlled trials, there was no significant difference in the overall survival (HR 0.98; 95% CI 0.82 to 1.18) and progression free survival (HR 1.01; 95% CI 0.87 to 1.17)between PCR and NACT group.[2]

The limitation of this study was that it was a retrospective study and all the data for evaluation were obtained from patient record files.All the files were not up to date and had missing data due to which they were excluded from the study. Moreover, there are no defined criteria for administering neoadjuvant chemotherapy for patients of advanced ovarian cancer, thus leading to selection bias in selecting the appropriate treatment method. Thus, administration of NACT is adopted by many clinicians to avoid aggressive primary surgeries to obtain optimal cytoreduction. Cases which were stage IIIC and higher were mostly opted for NACT followed by ICR which resulted in limited cases of PCR. The other limitation of the study was that the two groups were not propensity matched.

Conclusion

The current study shows that NACT followed by ICR has better survival outcomes than PCR. However, this data cannot be generalized and requires further propensity matched prospective studies. Complete resection of all macroscopic disease, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the objective whenever cytoreductive surgery is performed. Moreover, NACT is valuable in obtaining optimal cytoreduction with less aggressive surgery. Thus, it is important to determine before and, the resectability of the tumor, which will consequently help in selecting the suitable treatment method for the patients.

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