

SURGICAL OUTCOME AFTER NEO-ADJUVANT CHEMOTHERAPY IN ADVANCED EPITHELIAL CARCINOMA OF THE OVARY

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ABSTRACT

The objective of this prospective study was to find out the surgical outcome/optimal cytoreduction after neo-adjuvant chemotherapy (NACT) in advanced epithelial carcinoma of the ovary (EOC). This study of EOC patients with stage III and stage IV (advanced stage) disease was carried out at Swat Institute of Nuclear Medicine, Oncology & Radiotherapy (SINOR) and Swat and Saidu Group of Teaching Hospitals (SGTH), Swat, Pakistan, from January 2017 to January 2021.

A total of fifty patients were treated with NACT followed by surgical cytoreduction. SPSS software was used to analyze optimal cytoreduction and overall radiological response rate to NACT.

The average age of the patients was 49.04±10.66 years. In marital status, 94% patients were married and family history of ovarian cancer was found positive in 10% patients. 56% patients were with stage III and 44% were with stage IV disease. After NACT radiological complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) was observed in 16%, 58%, 20% and 6% patients respectively. Optimal surgical cytoreduction was achieved in 70% patients. NACT in advanced epithelial carcinoma of the ovary showed good promising surgical results. NACT improved patient's quality of life by minimizing more invasive surgical procedure.

Key-words: Neoadjuvant chemotherapy, optimal cytoreduction, primary debulking surgery, epithelial ovarian carcinoma.

INTRODUCTION

Ovarian cancer is one of the gynecology malignant tumor associated with high mortality (Partridge & Barnes, 1999). It is originated from epithelium or stromal cells of the ovary (Du Bois *et al.*, 2009; Ovarialkarzinom, 2009). Seventy percent of ovarian cancer is of epithelial origin. Ovarian cancer cells have the tendency to spread or metastasize to other organs of the body like liver, lungs, lymph nodes and abdominal lining etc. (Ebell *et al.*, 2016). It can be differentiated into different stages as per Federation of International Gynecologists and Obstetricians (FIGO) staging criteria (Du Bois *et al.*, 2009). In initial stages of this cancer, there may be minor or no specific symptoms and approximately 80 percent of cases are presented with stage III and IV diseases at the time of clinical examination (Siegel *et al.*, 2014). Biopsy of ovary or ascetic fluid can be used for diagnosis of disease and further investigation workup can be needed for staging status i.e. serological finding (tumor marker CA-125), radiological findings (pelvic ultrasound, abdominal and pelvic CT scan with contrast) along with clinical and histological findings (Balestreri *et al.*, 2002; Jacobs *et al.*, 1990; Ricke *et al.*, 2003). For metastasis and diffuse carcinomatosis chest x-ray, mammography and endoscopy are recommended (Siegel, 2014). From epidemiologic point of view research studies has reported that it accounts for 4% of all female sex organ mutation tumors, 31% of female genital cancer and 5% of cancer deaths (Eisenkop *et al.*, 1992; Frei III, 1982). The risk of women developing ovarian cancer during their lives is about 1.5% (Jacobs *et al.*, 1990). Advanced ovarian cancer is associated with high mortality rate and has less than 40% 5-year overall survival (Seidman *et al.*, 2012). Primary debulking surgery of ovarian tumor followed by Carboplatin and Paclitaxel based chemotherapy is currently standard treatment for patients with early stage I, II and in some patients with early stage III disease (Bristow *et al.*, 2002; Vergote *et al.*, 2010).

Recently, NACT has been introduced for patients with advanced ovarian cancer aiming to improve patient survival rates (Frei III, 1982). In this study response to NACT was evaluated through enhanced CT with contrast scan of the abdomen and pelvis, done four week after completion of three to six chemotherapy cycles using modified WHO response criteria. The radiological response was categorized as complete response (CR), partial

response (PR), stable disease (SD), and progressive disease (PD) (Miller *et al.*, 1981). The role of NACT was evaluated in advanced epithelial ovarian cancer with respect to response rate, resectability rate, and extent of optimal cytoreduction during debulking surgery in Khyber Pakhtunkhwa population, with a view to improve patient surgical outcome.

MATERIALS AND METHODS

This prospective based study was conducted at SINOR and SGTH, Swat Pakistan. Advanced epithelial ovarian carcinoma (EOC) patients with informed consent and with age less than seventy years were included in the study. The patients received chemotherapy at SINOR hospital, Swat. Each patient was evaluated with detailed history of the symptoms and comprehensive physical examination (Balestreri *et al.*, 2002; Jacobs *et al.*, 1990). Radiological examination of patients (ultrasound, CT scan / MRI) was done to assess the extent of disease and staging's evaluation. Chemotherapy was started after clinical/ radiological staging. The serum level of CA 125 in each patient was measured on presentation and after NACT of 3 and 6 cycles, to evaluate biological response to the NACT (Hou *et al.*, 2007). According to the established protocol, chemotherapy (Paclitaxel + Carboplatin) was administered after every 21 day. In our study, this chemotherapy protocol was given to 100% patients. Response to NACT was evaluated through clinical, serological and radiological findings using modified WHO response criteria (Miller *et al.*, 1981). The patients, who achieved complete and partial response, were referred to Gynae & Obs department of SGTH, Swat for surgical procedure. Total Abdominal Hysterectomy (TAH) and Bilateral Salpingoophorectomy (BSO) was done, however Omentectomy was also done in rare cases. In some cases where tumor was still inoperable (stable disease), additional 3 cycles were given to the patients according to protocol to achieve maximum response. 2nd line chemotherapy was started to progressive disease patients. Mean was calculated for quantitative variables like age, BMI, number of cycles of chemotherapy and CA 125. Frequency and percentages were calculated for tumor grade, stage of disease and surgical outcome (tumor size). Variables like age, BMI, durations, stage of disease and number of cycles was controlled through stratification.

RESULTS

The average age of the patients was 49.04 ± 10.66 with range (31-69) years. Out of 50 patients 6% were unmarried while 94% were married. Thirty percent females were nulliparous, 22% had parity 1, 20% had parity 2 and 28% had parity 3. The mean BMI of the patients was 31.87 ± 6.78 with range (20.4 ± 44.78) kg/m². Positive family history (FH) of ovarian cancer was found in 5(10%) patients. As per FIGO criteria, 56% patients were with stage III and 44% patients were with stage IV cancer. Three cycles of chemotherapy was given to 48% patients and six cycles were given to 52% patients. After NACT down staging status, 16%, 36%, 28% and 20% patients were found with stage I, II, III, and IV respectively shown in Table 1.

Table 1. Comparison of stage of cancer after NACT in age groups, marital status and parity.

		Stage of cancer after NACT				Total
		I	II	III	IV	
Age	≤50	4	9	9	4	26
		15.4%	34.6%	34.6%	15.4%	100.0%
	>50	4	9	5	6	24
		16.7%	37.5%	20.8%	25.0%	100.0%
Marital Status	Married	7	17	13	10	47
		14.9%	36.2%	27.7%	21.3%	100.0%
	Unmarried	1	1	1	0	3
		33.3%	33.3%	33.3%	0.0%	100.0%
Parity	Null & Primary	4	9	8	5	26
		15.4%	34.6%	30.8%	19.2%	100.0%
	Multiple	4	9	6	5	24
		16.7%	37.5%	25.0%	20.8%	100.0%

Table 1 shows that there is statistically insignificant difference found between the stages of cancer after NACT in age groups, marital status and parity.

After NACT (WHO response criteria) radiological CR (Complete response), PR (Partial response), SD (Stable disease) and PD (Progressive disease) was 16%, 58%, 20% and 6% in the patients, respectively as shown in Table 2.

Table 2. Base-line and post-chemotherapy sizes of index lesions in the patients with CR, PR, SD and PD.

S.NO	Patient with different responses	No of patients	mean base-line size of index lesion	Mean post chemotherapy mean base line size index	Mean % decrease & increase in base line size index lesion in PD
1	CR	08	30.2 ± 6.4cm ²	0 cm ²	100%
2	PR	29	60.5 ± 23cm ²	16.65± 58cm ²	68.27%
3	SD	10	87.12± 12cm ²	71 ± 12cm ²	27.3%
4	PD	3	13 ± 21cm ²	24 ± 41cm ²	63.3%

Table 2 shows mean base-line and post-chemotherapy sizes of index lesions before and after NACT in all patients. The same response in detail for the patients having CR (Complete response), PR (Partial response), SD (Stable disease) and PD (Progressive disease) are also demonstrated graphically in the following Fig. 1.

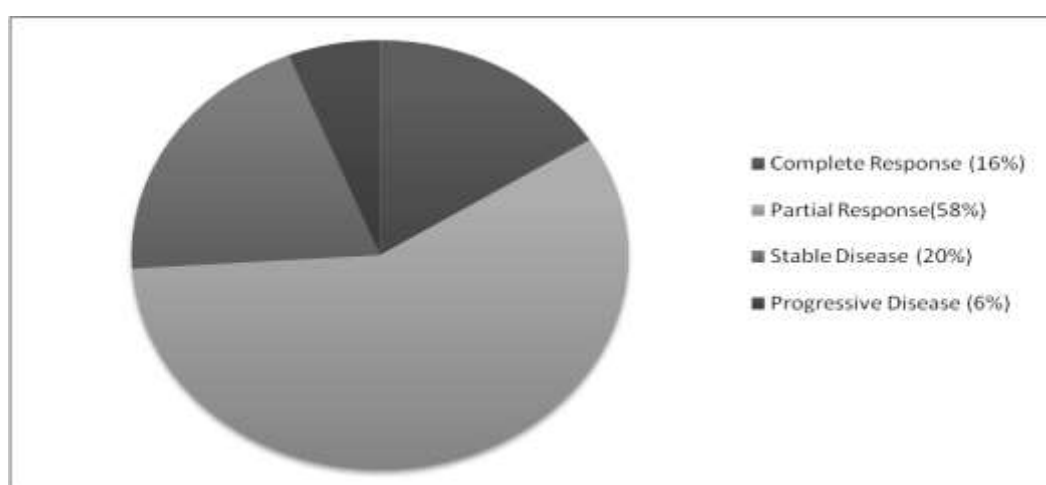


Fig.1. Percent response of number of patient to NACT.

BMI, FH of the cancer, stage before the NACT and number of chemotherapy cycles for all patients are shown in the table 3.

Table 3. BMI, FH of the cancer, stage before the treatment and number of chemotherapy cycles for all patients.

		Stage of cancer after treatment				Total
		I	II	III	IV	
BMI	≤25	3 33.3%	3 33.3%	3 33.3%	0 0.0%	9 100.0%
	>25	5 12.2%	15 36.6%	11 26.8%	10 24.4%	41 100.0%
Family history of cancer	Positive	2 40.0%	0 0.0%	2 40.0%	1 20.0%	5 100.0%
	Negative	6 13.3%	18 40.0%	12 26.7%	9 20.0%	45 100.0%
Stage before treatment	III	8 28.6%	15 53.6%	5 17.9%	0 0.0%	28 100.0%
	IV	0 0.0%	3 13.6%	9 40.9%	10 45.5%	22 100.0%
Cycles	3	3 12.5%	5 20.8%	6 25.0%	10 41.7%	24 100.0%
		5 19.2%	13 50.0%	8 30.8%	0 0.0%	26 100.0%
	6	3 12.5%	5 20.8%	6 25.0%	10 41.7%	24 100.0%
		5 19.2%	13 50.0%	8 30.8%	0 0.0%	26 100.0%

Comparison of residual less than 1 cm for all patients after treatment, with respect to number of cycles is mentioned in Table 4.

Table 4. Comparison of residual <1 cm after treatment between cycles of the treatment.

		Residual<1cm		Total	p-value
		Yes	No		
Cycles	3	9 37.5%	15 62.5%	24 100.0%	<0.001
	6	26 100.0%	0 0.0%	26 100.0%	
Total		35 70.0%	15 30.0%	50 100.0%	

Among patients having 3 cycle of treatment the residual <1 cm was found in 9 (37.5%) patients whereas among patients having 6 cycles of treatment the residual <1 cm was found in 26(100%) patients. This difference was statistically significant i.e. p-value = <0.001.

The average value of Ca-125 before and after NACT for all patients is 274.44 (75, 639) and 39.76 (10, 98), respectively as shown in Fig.2.

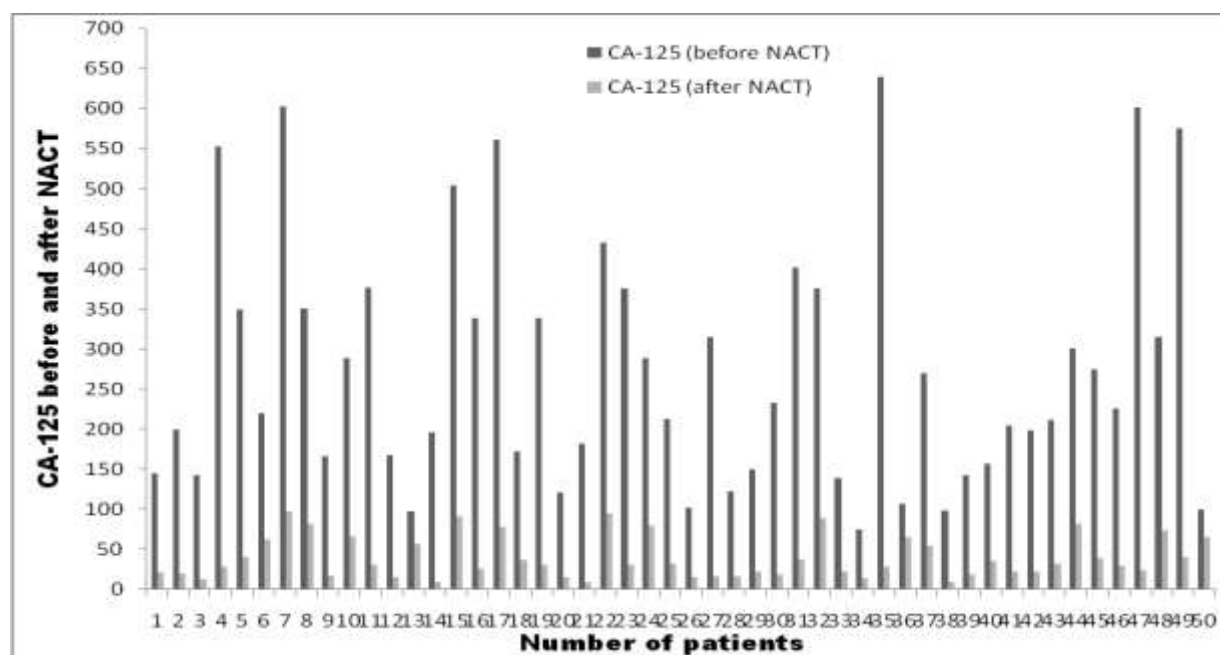


Fig.2. Graph between number of patients and Ca-125 before and after NACT.

DISCUSSION

Ovarian cancer patient mostly presented in advance stage with bad prognosis, OS is less than 40% because sign, and symptoms usually appear very late. Successful treatment of advanced stage EOC still remain a challenge and need more work to improve patient quality of life (QOL) and survival. Bristow *et al* meta-analysis stated that after primary surgery poor prognosis is associated with residual tumor more than 2 cm (Frei III, 1982). Research proves that patients with advanced stage ovarian cancer cannot achieve optimal surgical cytoreduction during primary surgery. In chemosensitive disease NACT has excellent role in reducing tumor burden, result in easier complete surgical cytoreduction (Chi *et al.*, 2010). NACT may be helpful in advanced stage ovarian cancer patients by achieving maximum cytoreduction to achieve residual tumor less than 1cm (Le *et al.*, 2005; Mazzeo *et al.*, 2003).

The rationale behind the use of NACT was to assess its role in down staging of locally advanced EOC. Optimal cytoreduction of tumor mass was achieved during surgery with no residual disease and less surgical intervention and morbidity. Radiological and clinical examination after NACT shows that stage I cancer patients

were 8(16%), stage II patients were 18(36%), stage III & stage IV cancer patients were 14(28%) & 10(20%) respectively. After NACT and surgery, residual <1cm was found in 70% patients, while radiological CR, PR, SD and PD was similar to the findings of (Ansquer *et al.* (2001); Chan *et al.* (2003); Le *et al.* (2005); Mazzeo *et al.*, (2003). In spite of more number of patients and more extensive disease response to NACT in our study is significantly higher as compare to above studies. Optimal cytoreduction (<1 cm) after NACT was similar to Ansquer *et al.* (2001); Chan *et al.* (2003); Le *et al.* (2005); Mazzeo *et al.* (2003). Decrease in serum level of CA125 was significant and was equal to the findings of (Le *et al.* (2007) We compared our study with randomized controlled trial conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore Pakistan, 15 patients were given NACT with following results: radiological CR, PR and SD were 25%, 29.4% , 4.2% patients, respectively and none of the patient had PD, whereas radiological response rate (RR) was 54.2% (Siddique *et al.*, 2010). In our study radiological RR after NACT was 64.71%, in comparison with another study which was conducted in India radiological RR after NACT was 52.2% (Siddique *et al.*, 2010). In our study Radiological RR were higher than above two studies, because we gave Carboplatin plus Paclitaxel chemotherapy regimen to 100% patient while in above two studies 94% and 77.8% patients received the same regimen and the remaining 6% and 22.2% patients received other chemotherapy combination with the same objective (Bilici *et al.*, 2010). Medina-Franco and Mejía-Fernández (2018) study results show that NACT trends toward higher QOL and lower rates of postoperative adverse events. Based on selected clinical features, NACT followed by surgical cytoreduction could be a reasonable alternative for those patients with reversible contraindications to primary surgery with objective of improving survival and QOL (Medina-Franco and Mejía-Fernández, 2018). Shimoji *et al.* reported a retrospective study of 51 cases with stage III and IV epithelial ovarian carcinoma treated in a hospital located in Japan. A total of 29 cases were treated with NACT followed by surgical cytoreduction and 22 with primary surgery. The NACT group achieved complete cytoreductive surgery (Shimoji *et al.*, 2017).

This study also support NACT followed surgery in EOC patients, as best option to treat them effectively and improving patients' QOL and reduce the financial burden.

CONCLUSION

NACT in Advanced EOC showed good promising surgical results. NACT is helpful in EOC by achieving maximum surgical cytoreduction result in residual tumor less than 1cm. NACT improved patient QOL by minimizing more invasive surgical procedure.

ETHICAL APPROVAL

Ethics Committee approval: SNOR-COD-01/2022.

PATIENTS' CONSENT

All participants provided informed consent before taking part in the study.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION

AH, STK, SA, BM, GB, JA: Conception, design, acquisition, analysis, and interpretation of data. AH, GB, HK, SS, JA, TN: Drafting and revising it critically for important intellectual content.: AH, STK, SA, BM, GB, JA, SS, HK, TN: Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors gave final approval of the version to be published.

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(Accepted for publication September 2023)