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Genitourinary Cancer

Is Optimal Cytoreduction Post Neoadjuvant Chemotherapy the Only Prognostic Factor in Advanced Ovarian Cancer?

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Abstract

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Background Epithelial ovarian cancer (EOC) is one of the leading causes of cancer-related death in women. Approximately 70% of patients with EOC are diagnosed in advanced stage [The International Federation of Gynecology and Obstetrics (FIGO stage III and IV)] with an expected 5-year survival rate of 30%. Numerous studies have shown that survival with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is noninferior to primary debulking surgery followed by chemotherapy.

Materials and Methods In this retroprospective observational study, 50 patients with advanced ovarian cancer, diagnosed from January 2012 to January 2015, were included and followed-up till January 2017. Correlation of NACT with patient profile, CA125 levels, clinicopathologic parameters, progression-free survival (PFS), and treatment response was studied. Statistical analysis was performed using log-rank test and Kaplan-Meir survival plots.

Results The extent of cytoreduction significantly correlated with PFS. The PFS was maximum in patients who had optimal cytoreduction (19 months) and 10 months in patients with suboptimal cytoreduction with p-value < 0.05. The survival was not significantly correlated with other parameters such as age, stage, preoperative CA125 levels, and ascites.

Conclusions The extent of cytoreduction following NACT in this study was associated with statistically significant PFS advantage in patients who were able to undergo optimal cytoreduction, but not significantly correlated to other factors such as age, stage, preoperative CA125 levels, and ascites. NACT followed by interval cytoreduction is an important modality affecting survival in advanced EOC. Further studies and longer follow-up are needed to demonstrate survival advantage over standard treatment.

Keywords

- epithelial ovarian cancer
- cytoreductive surgery
- interval debulking surgery
- neoadjuvant chemotherapy
- progression-free survival

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Introduction

Epithelial ovarian cancer (EOC) is one of the leading causes of cancer-related death in women.[1] Approximately 90% of ovarian cancers are epithelial in origin; nearly 70% of patients with EOC cancer are diagnosed in advanced stage (FIGO stage III and IV),[2] which is associated with high morbidity and mortality and an expected 5-year survival rate of 30%.[3] Ovarian cancer is the seventh most common cancer in women worldwide.[4] There has been statistically significant improvement in 5-year survival rates over the decades, which was 36% in 1977 and improved to 45% in 2002.[5] The improvement in survival is primarily due to improved and effective chemotherapeutics and better surgical techniques.

The treatment of advanced ovarian cancer is challenging. In the last decade, number of studies and published literature have highlighted the usefulness of upfront chemotherapy followed by interval cytoreduction as an important treatment modality in advanced ovarian cancer. The survival with neoadjuvant chemotherapy (NACT) is noninferior to primary debulking surgery followed by chemotherapy. There has been a significant increase in the incidence of ovarian cancer as has been reported in various population-based cancer registries (PBCRs). The PBCRs at Bangalore, Chennai, Delhi, and Mumbai showed statistically significant annual percentage increase in occurrence of ovarian cancer, which was 2.04, 1.56, 0.98, and 0.86%, respectively.[9] In India, 26, 834 cases of ovarian cancer were reported in 2012 with a crude incidence rate of 4.4 and ASR of 4.9 for incidence. Among the Asian countries, maximum number of deaths due to ovarian cancer occurred in India in 2012 (19,549 cases). The crude mortality rate of 3.2 and ASR of 3.6 for mortality were estimated for year 2012.[10]

Objective of this retroprospective observational study was to study the impact of NACT on progression-free survival (PFS) in advanced ovarian cancer patients.

Prognostic Factors for Epithelial Ovarian Cancer

The factors associated with adverse prognosis are age, stage at diagnosis, Eastern Co-operative Oncology Group (ECOG) performance status, histology, platinum sensitive or resistant relapse (less than 6 months), poor PS, mucinous histology, larger number of sites of disease, and CA125 levels.

Treatment of Advanced Stage (FIGO Stage III and IV)

The surgical management with primary debulking is performed in surgically fit patients. The main goal of debulking is to remove all the gross disease. The patients deemed poor candidates due to the advanced age, poor ECOG performance status, or co morbidities and high disease burden are usually treated with chemotherapy followed by interval debulking surgery (IDS) followed by postoperative chemotherapy. The choice of chemotherapy is a platinum compound combined with a taxane (paclitaxel). Various regimens have been used (weekly dose dense or thrice weekly schedule). The combination of paclitaxel, carboplatin, and bevacizumab can be used as upfront chemotherapy only with caution due to risk of perforation and hemorrhage. The experience of treating advanced ovarian cancer with platinum compounds dates back to late 1970s. The combinations of both cisplatin and carboplatin have been used to treat advanced ovarian cancer since last 15 years. It is now clear that paclitaxel plus cisplatin is superior to cisplatin and cyclophosphamide combination on the basis of Gynecologic Oncology Group's (GOG's) GOG 111 results.[11] In 2003, du Bois et al showed paclitaxel plus carboplatin to be equivalent to paclitaxel plus cisplatin.[12]

Numbers of trials have been performed by adding doxorubicin to cyclophosphamide and cisplatin combination, but none of these has shown improvement in overall survival. Another phase III trial (GOG 182) showed no advantage of adding pegylated liposomal doxorubicin, topotecan, or gemcitabine to paclitaxel plus carboplatin combination.[13]

Various trials have studied the utility of bevacizumab (anti-VEGF) in both frontline and relapsed settings. The two dosing schedules have been evaluated (7.5 mg and 15 mg) in patients with high-risk stage III and IV EOC. It has been used for a period of 1 year to 15 months.[14,15]

PARP inhibitors olaparib and rucaparib have been approved for ovarian cancer patients with BRCA mutation who have received three or more lines of chemotherapy.[16–18]

According to GOG, optimal cytoreduction refers to the residual disease that is $\leq$1 cm in maximum tumor diameter. Suboptimal cytoreduction refers to the residual tumor nodule of $>$1 cm size. The importance of defining extent of cytoreduction lies in the fact that the extent of cytoreduction correlates with survival. It is now clear that better outcomes are noticed in patients with optimal cytoreduction as compared to suboptimal cytoreduction.

The survival advantage was also demonstrated with complete CRS and platinum/taxane-based chemotherapy in a meta-analysis of 18 studies (retrospective and prospective studies) involving patients with stage IIB or higher.

The commonly used selection criteria for NACT include stage IV disease, large volume ascites ($>$1,000 mL), bulky ($>$1–2 cm) disease in upper abdomen, omental extension to spleen, suprarenal adenopathy, parenchymal liver disease, diaphragmatic disease, and peritoneal carcinomatosis.

Study Rationale

This retroprospective study was done to investigate the response to NACT in PFS among ovarian cancer patients presenting at an advanced stage (FIGO stage III and IV). Other parameters such as proportion of patients able to undergo optimal cytoreduction following NACT, age distribution, histology, CA125, and ascites were also studied. The advanced EOC is one of the leading causes of cancer-related death among women. The primary treatment traditionally has been cytoreductive surgery followed by chemotherapy. There has been little improvement in overall survival despite radical surgeries and use of newer chemotherapeutic drugs; multiple trials have demonstrated equivalent survival in

advanced ovarian cancer patients treated with NACT followed by IDS. Various studies have also shown that optimal cytoreductive surgery is an important and modifiable prognostic factor. NACT thus helps to achieve optimal cytoreductive surgery translating into better PFS and overall survival.

Aims

1. To assess the PFS in advanced ovarian cancer following NACT (paclitaxel and carboplatin).
2. To assess the response to NACT in advanced ovarian cancer.

Settings and Design

Methods and Material

In this retroprospective study, 50 patients with advanced ovarian cancer, histopathologically diagnosed from January 2012 to January 2015, were included and followed-up till January 2017.

Correlation of NACT with patient profile, CA125 levels, clincopathologic parameters, PFS, and treatment response was studied.

Statistical analysis used: log-rank test and Kaplan-Meir survival plots.

Results

Majority (23; 46%) patients were in 51 to 60 years age group followed by patients older than 60 years (34%). The number of patients with age 50 years or lesser was 10 (20%). Median PFS in patients with age 50 years or less was 17.7 months, 13.7 months in 51 to 60 years age group, and 15.1 months in patients aged 61 years or more. The *p*-value was 0.25 (not significant).

The number of patients presenting in stage III was 36 (72%), while 14 (28%) patients presented in stage IV. Median PFS in stage III patients was 17.6 months as compared to 12.1 months in stage IV patients, and the difference was statistically not significant ($p = 0.69$).

The predominant histology noticed in this study was adenocarcinoma, which was observed in 43 (86%) patients; other histologies were noticed in the remaining 7 (14%) patients.

CA125 levels at presentation were elevated in all the 50 (100%) patients, levels less than or equal to 100 units/mL were observed in 3 (6%) patients, levels between 100 and 1,000 units/mL were observed in 22 (44%) patients, 1,001 to 5,000 units/mL were seen in 19 (38%) patients, and levels more than 5,000 units/mL were seen in 6 (12%) patients. Median PFS was 15.1 months in patients with CA125 less than or equal to 100, 13.0 months in patients with CA125 levels 101 to 1,000, 13.7 in patients with CA125 levels 1,001 to 5,000, and 14.9 months in patients with CA125 levels more than 5,000, and the difference in PFS was statistically insignificant ($p = 0.63$).

The most consistent clinical finding in this study was presence of ascites, which was observed in 46 (92%) patients while it was absent in 4 (8%) patients. The observed PFS in patients with ascites was 14.9 months and 12.1 months in patients without ascites. The difference observed in PFS was not statistically significant ($p = 0.80$).

Response assessment according to RECIST 1.1 showed partial response in 43 (86%) patients, stable disease in 3 (6%) patients, and progressive disease in 4 (8%) patients. The PFS in patients achieving partial response was 15.1 months, 12.1 months in patients with stable disease, and 10.3 months in patients with progressive disease. The observed difference was statistically not significant ($p = 0.17$).

PFS was also influenced by the completeness of surgery. Six patients (12%) did not undergo surgery due to various reasons, optimal CRS was feasible in 33 (66%) patients, and 11 (22%) underwent suboptimal CRS. The PFS was maximum (19 months) in optimally cytoreduced patients followed by patients undergoing suboptimal cytoreduction (10 months) and 9.8 months in patients who were not candidates for cytoreductive surgery. The result was statistically significant ($p < 0.05$; ►Fig. 1).

Discussion

In this study, the response to NACT, extent of cytoreduction in response to treatment, and PFS with NACT/IDS in patients with advanced ovarian cancer (stage III and IV) were studied. The association of other variables such as age, stage, ascites, and CA125 levels with PFS was also studied.

Patient Profile in the Study

Fifty patients, who fulfilled the inclusion criteria, were included in the study. Only 3 (6%) patients were premenopausal and remaining 47 (94%) had attained the menopause. Family history of ovarian cancer could not be identified in any of the patients. The main presenting symptom in the present study was abdominal distension, which was present in 46 (92%) patients; other common symptoms were pain abdomen and early satiety. All the patients received paclitaxel (175 mg/m^2) plus carboplatin (AUC = 5) as NACT.

The overall median PFS in this study was 14.9 months (95% confidence interval: 11.17–18.62 months), which is similar to that observed by Kumar et al in their prospective randomized study.[19]

Distribution of Histopathology Features in the Study

Most common histopathological subtype in this study was adenocarcinoma (43, 86%); other histologies were noticed in the remaining seven patients including one patient with transitional cell carcinoma of the ovary. Of these, 6 (12%) had poorly differentiated carcinoma. Adenocarcinoma "not otherwise specified" was observed in 38 (76%) patients. Papillary variant was seen in 4 (8%) and mucinous variant was observed in 1 (2%).

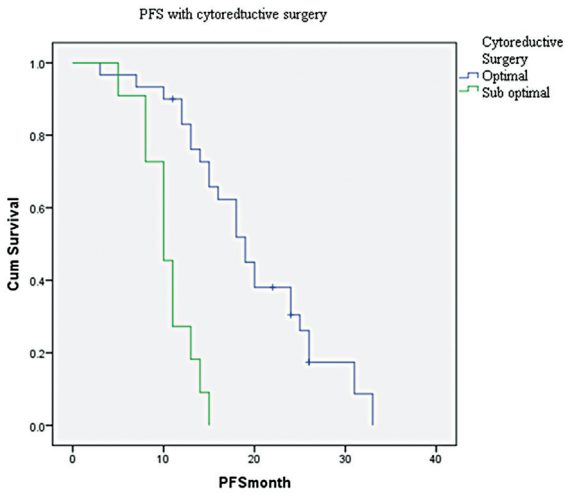

Fig. 1 Kaplan Meir survival curve showing PFS with cytoreductive surgery.

Metastatic Pattern

Stage IV disease was seen in 14 (28%) patients. Pleura was the commonest site of metastasis observed in 9 (18%) patients followed by liver in 3 (6%) patients and other extra-abdominal sites in 2 (4%) patients.

PFS in patients with age 50 years or less was 17.7 months, 13.7 months in 51 to 60 years age group, and 15.1 months in patients aged 61 years or more. The *p*-value was 0.25 (not significant). In this study, the survival was highest in patients less than 50 years of age indicating that the younger age at diagnosis is associated with better PFS, which is similar to the survival observed in GOG group study and other studies,[20,21] though this difference in PFS among the groups was not statistically significant. This finding can be explained by the fact that the sample size of the study was small, and only 10 patients were aged 50 years or less.

The PFS was higher in stage III (17.6 months) patients as compared to stage IV patients in whom it was 12.1 months. The difference in survival did not achieve statistical significance, which may be due to small size of the study. The 1998 FIGO annual report also suggests that the patients with stage IV have lesser survival (11%) as compared to stage III patients treated similarly (survival 25%).[22]

Ascites was noticed in 46 (92%) patients, and PFS was comparable in patients with ascites and in patients without ascites with no statistically significant difference among the groups (14.9 versus 12.1 months, $p = 0.80$). The survival was higher in patients with ascites group; this might be confounded due to smaller number of patients without ascites in this study. The presence of ascites is a definite prognostic factor in early ovarian cancer; its role as prognostic factor in advanced stage disease is not clearly defined. Xu et al in their retrospective study observed that regression of ascites to less than 500 mL after NACT was associated with a PFS of 19.7 months, indicating that regression of ascites is better predictor of survival.[23]

The PFS was highest in patients with CA125 less than 100 U/mL (15.1 months). There was not found statistically

Table 1 Progression-free survival with level of significance with different variables

S. no	Parameter		Number	Percentage (%)	Median PFS (months)	*p*-Value
1.	Age (years)	≤50	10	20	17.7	0.25
		51–60	23	46	13.7	
		≥61	17	34	15.1	
2.	Stage	III	36	72	17.6	0.69
		IV	14	28	12.1	
3.	Histopathology	Adenocarcinoma	43	86		
		Others	7	14		
4.	Preoperative CA125 levels (units/mL)	≤100	3	6	15	0.63
		101–1,000	22	44	13	
		1,001–5,000	19	38	13.7	
		>5,000	6	12	14.9	
5.	Ascites	Present	46	92	14.1	0.80
		Absent	4	8	12.9	
6.	Response (RECIST 1.1)	PR	43	86	15	0.17
		SD	3	6	12.1	
		PD	4	8	10.3	
7.	Cytoreductive surgery	Optimal	33	66	19	<0.05
		Suboptimal	11	22	10.0	
		No surgery	6	12	98.8	

Abbreviations: CA, Cancer Antigen; PD, Progressive Disease; PFS, Progression-free survival; PR, Partial Response; SD, Stable Disease.

significant difference in PFS between the groups. Various studies have shown that preoperative CA125 levels do not correlate with survival.[24,25] Gronlund et al in their prospective study of 70 patients concluded that preoperative CA125 levels did not affect survival by any cutoff value.[24]

In this study, following were the response to NACT after completion of three cycles, according to RECIST 1.1: 43 patients achieved PR, 3 patients SD, and 4 patients had progressive disease with PFS of 15.1, 12.1, and 10.3 months, respectively. Patients with partial response achieved better PFS as compared to the other two groups, but the difference in survival was not statistically significant. The response rates observed in this study are similar to those observed in a retrospective study conducted by Baruah et al who observed similar overall response rate of 95.19% (96% in this study).[26]

The number of patients in this study who were able to undergo optimal cytoreduction was 33 (66%), 11 (22%) patients underwent suboptimal CRS, and 6 (12%) patients were not considered for surgery. The PFS was 19 months in optimal cytoreduction group, 10 months in suboptimal cytoreduction group, and 9.8 months in patients who did not undergo cytoreductive surgery. The difference was statistically significant with p-value <0.05. This clearly highlights the fact that patients who are able to undergo optimal cytoreduction after NACT have the best outcome. This finding is supported by the published literature, and further supported by a prospective study published in *Obstetrics and Gynecology International* in which survival benefit of 5 months was observed in patients who underwent IDS after receiving NACT compared to those who were treated with primary debulking surgery followed by chemotherapy.[27]

Conclusions

There are numerous randomized trials, retrospective series, observational studies, and meta-analyses that have demonstrated the noninferiority of NACT with IDS to primary debulking surgery followed by chemotherapy, which has been the standard of care for many years. The inherent differing histological subtypes, biological behavior, molecular characteristics, and chemo responsiveness may affect the outcome in the advanced ovarian cancer. The patients who undergo optimal cytoreduction following NACT have a survival advantage.

The extent of cytoreduction in this study was associated with statistically significant PFS in patients who were able to undergo optimal cytoreduction, but not significantly correlated to other factors such as age, stage, ascites, and preoperative CA125 levels.

It signifies the fact that NACT followed by interval cytoreduction is an important modality affecting survival in advanced EOC. Further studies and longer follow-up are needed to demonstrate survival advantage over standard treatment.

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None.

Conflict of Interest
None declared.

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