Article published online: 2023-08-07

Gynaecological Cancer

Critical Analysis of Advanced High-Grade Serous Epithelial Ovarian Cancer in Women: An Experience of 100 Cases from a Regional Cancer Center in Northeast India

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South Asian J Cancer 2023;12(4):334–340.

Abstract

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Ovarian cancer is the sixth most common cancer in women worldwide. Patients with ovarian carcinoma mostly present at an advanced stage with serous type of epithelial ovarian cancers, which is the most lethal of all pelvic malignancies. This study aims to critically analyze high-grade serous epithelial ovarian carcinomas in women from the Northeastern region of India and compare our data with Western literature to modify treatment strategies and improve survival outcomes. This hospital-based retrospective analysis involved data from the records of 100 women with high-grade epithelial ovarian cancer treated primarily with neoadjuvant chemotherapy followed by interval debulking surgery in the department of gynecologic oncology at a tertiary level regional cancer institute from January 2018 to December 2019. The demographic, clinical and pathological profile, and survival outcome were evaluated using descriptive statistics. The overall survival of the study population was calculated using Kaplan–Meier curves using SPSS software (version 24). The majority of women belonged to 41 to 55 years age group. At first presentation to the hospital, 89 and11% patients were in stage III and stage IV of disease, respectively. Clinically, 95% of women had ascites, and 18% had metastasis to lymph nodes. Distant metastasis to lungs and liver was present in 10 and 3% of cases, respectively. A substantial percentage (98%) of women had raised serum Ca125 > 1000 at baseline, ranging from 1,745 to 10,987 IU/mL. Almost two-thirds of the cases had partial-to-complete response to neoadjuvant chemotherapy (78%). In most of the women (72%), there was no residual disease at interval debulking surgery (R0), though 28% women had R1& R2 resection. The median overall survival time was 36 months. High-grade serous ovarian cancer is commonly seen in older age group, but its occurrence in younger population has also been observed. Early diagnosis is crucial in decreasing morbidity and mortality among these patients.

Keywords

- Ca125
- epithelial ovarian cancer
- interval debulking surgery
- neoadjuvant chemotherapy
- overall survival

DOI https://doi.org/10.1055/s-0043-1771444 ISSN 2278-330X

How to cite this article: Barmon D, Patra S, Nandwani M, Jethani R, KatakiA.C., et al. Critical Analysis of Advanced High-Grade Serous Epithelial Ovarian Cancer in Women: An Experience of 100 Cases from a Regional Cancer Center in Northeast India. South Asian J Cancer 2023;12(4):334–340.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Therefore, efforts should be made to identify risk factors for malignancy. Assessing each parameter of statistical information reflecting its own profile may be important for calculating the risk for the development of ovarian cancer, which can help in implementing preventive measures in the future.

Introduction

Ovarian cancer is the sixth most common cancer in women worldwide and is the leading cause of death of all gynecological cancers. Patients of ovarian carcinoma mostly present at an advanced stage at primary presentation with serous type of epithelial ovarian cancers (EOCs), which are the most lethal of all pelvic malignancies. The overall survival (OS) for advanced stage disease has been reported as 5 to 30%.[1] High recurrence rates between 60 and 85% within 5 years are typical for this disease even after primary treatment.[2–4] The prognosis of advanced ovarian cancer with such high recurrence rate is reported to be very poor with a median survival time of less than 2 years.[5]

Because EOC has almost no early onset of symptoms and its current screening is difficult to be performed in the general population, nearly 80% of EOC patients are diagnosed during the last stage of the disease. Most of the advanced EOC patients are treated either with cytoreductive surgery combined with platinum-based chemotherapy or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Twenty to thirty percent of these patients are able to survive a period that is not exceeding 2 years and another 15% of patients are able to obtain a 10 years survival.[5–8]

We undertook this study to critically analyze women with high-grade serous epithelial ovarian carcinomas and to study its survival in the Northeastern region of India and to compare our data with the Western literature that can help us in modifying treatment strategies to improve survival outcomes.

Materials and Methods

Women with high-grade EOC treated in department of gynecologic oncology at a tertiary level regional cancer institute of Northeast India from January 2018 to December 2019 were evaluated. The total number of cases of ovarian cancer during the study period were 549, out of these a lot of cases were lost to follow-up or records could not be retrieved as it was a retrospective study. So, we analyzed 100 cases who were in regular follow-up and whose all records and investigation results were available.

It was a hospital-based retrospective study of 100 cases collected via convenient sampling method based on average number of patients with ovarian tumor annually. The study included patients with high-grade serous epithelial ovarian tumors and those who were on regular follow-up. Women with other histopathologies, primary peritoneal carcinomatosis, and missing data, treated outside, were excluded from the study.

All cases underwent three to four cycles of NACT followed by IDS). The response evaluation after NACT was scored according to Response evaluation criteria in solid tumors (RECIST) criteria.[6] The type of resection during IDS was labelled as R0, R1, and R2 based upon the residual disease left behind (**Box 1**).

All women completed their chemotherapy cycles post-surgery. These women were then followed up 3 monthly for first 2 years, 6 monthly for the next 3 years, and annually thereafter. At each visit, they were monitored on the basis of clinical symptoms, clinical examination, and serum Ca125 levels for disease recurrence.

OS was defined as the length of time from diagnosis to death, or to the last follow-up examination of patients who were still alive.

Statistical Analysis

The demographic and clinical parameters for all patients were evaluated using descriptive statistics. The OS of the study population was calculated using Kaplan–Meier curves. SPSS software, version 24, was used for the same.

Results and Observations

The demographic and clinical characteristics of the study population were analyzed (►**Table 1**). Majority of the women belonged to 41 to 55 years age group, in which 61% of women were postmenopausal. At first presentation, 89% and 11% women were in stage III and stage IV of disease respectively. Clinically, 95% of women had ascites, and 18% had metastasis to lymph nodes (18%). Distant metastasis to lungs and liver was present in 10% and 3%, respectively. A substantial percentage (98%) of women had raised serum Ca125 > 1000 at baseline, ranging from 1745 to 10, 987 IU/mL. The median baseline serum Ca125 was 4537 that ranged from 1745 to 10, 987 IU/mL. Almost all women (100%) had Ca125 levels > 1000.

Post-NACT response was evaluated based on clinical examination, imaging and biochemical tests (►**Table 2**). Almost two-third of the women had partial-to-complete response to NACT as per RECIST criteria (78%). Clinical response was seen as disappearance of ascites (72%) and a fall in serum Ca125 levels to normal (42%, median =46 IU/mL). None of the

Box 1 Residual disease after surgery

Residual disease after surgery	
R0	No macroscopic residual disease
R1	Macroscopic residual disease with a maximal diameter of <1 cm
R2	Macroscopic residual disease with a maximal diameter of >1 cm

Table 1 Baseline characteristics of study population

Baseline characteristics	Number (100)	Percentage (%)
Age (years)		
25–40	24	24
41–55	56	56
> 55	20	20
Mean ± SD) (in years) Range Median	47.8 ± 10.3 25–71 48	
Menopausal status		
Premenopause	39	39
Postmenopause	61	61
Stage of the disease		
III	89	89
IV	11	11

Abbreviation: SD, standard deviation.

Table 2 Distribution of cases based on the post-NACT clinical response ($n = 100$)

Clinical parameters	*n*	Percentage
Ascites		
Yes	28	28
No	72	72
Ca125		
< 35	42	42
> 35	58	58
Imaging based on RECIST criteria		
Complete	3	3
Partial	75	75
Stable	22	22

Abbreviation: NACT, neoadjuvant chemotherapy.

women showed disease progression post-NACT. At IDS, type of resection and post-IDS histopathological examination of resected specimen were reviewed (►Table 3). The type of resection at IDS was R0 in 72% and R1, R2 in 28%. The histopathological examination of the specimen revealed presence of residual tumor in the ovary and omentum in 88% and 72% respectively, though only 10% demonstrated no tumor in the resected specimen (ovary or omentum). Thus, the complete response (CR) to chemotherapy in the ovary and omentum was seen in 12 and 28%, respectively.

The postoperative (post-IDS), biochemical parameters revealed a significant fall in the serum Ca125 levels (►Table 4). The mean serum Ca125 was 36.9 ± 64.76 IU/mL, varying between 5 and 448 IU/mL. Majority of the women showed a normal level of less than 35 (80%).

We also analyzed the time interval between NACT-IDS and IDS-adjuvant CT. Mean time interval from the end of

Table 3 Distribution of cases according to type of resection at IDS and pathological response based on CRS ($n = 100$)

Type of resection at IDS	Number	Percentage
R0	72	72
R1	19	19
R2	9	9
Pathological response (chemo response score)		
Presence of disease (ovary, omentum, peritoneum /organs)	90	90
Absence of residual disease (ovary,		
omentum, peritoneum)	10	10
Ovary		
1	59	59
2	29	29
3	12	12
Omentum		
1	69	69
2	2	2
3	29	29
Peritoneal deposits		
0	50	50
1	50	50
Others		
0	64	64
1	36	36

Abbreviations: CRS, cytoreductive surgery; IDS, interval debulking surgery.

NACT to adjuvant CT was 7.7 ± 1.82 weeks ranging from 5 to 16 weeks; the mean time interval from NACT-IDS and IDS-adjuvant CT was 3.8 weeks each side.

Among the 100 women, 29% patients had recurrence at 6 months, 33% at 6 to 12, 21% after 12 months, and 16% had recurrence after 24 months time. The median time to recurrence in the cohorts was 10 months with a mean of 15.3 months ranging from as early as 2 months to as late as 96 months. Nearly 50% women had relapse beyond 1 year, though in one-third of cases, the disease relapsed within 6 months time.

The OS at the end of 1 year was 98%, which decreased significantly to 49% at the end of 3 years. The 5-year OS was 33% (►Fig. 1). The median OS time was 36 months (95% confidence interval [CI]: 30–41.9). On the other hand, the survival post-recurrence also showed a significant decrease from 57% at 1 year to 30 and 26% at the end of 3 and 5 years. The median recurrence to survival time was 17 months (95% CI: 11.9–22.077; ►Fig. 2). The patients who suffered a recurrence did receive second-line chemotherapy and salvage treatment based upon the site of recurrence, burden of disease, biochemical parameters, and performance status of the patient.

Table 4 Distribution of cases on the biochemical characteristics (post-IDS) ($n = 100$)

Biochemical variables post-IDS		*n*	Percentage (%)
Post IDS Ca125			
< 35	83		83
35–200	13		13
200–500	4		4
Mean ± SD (IU/mL) Range Median		36.9 ± 64.76 5–448 20	
Neutrophil–lymphocyte ratio			
≤1	61		61
> 1	39		39
Post IDS PLR			
≤5.0	53		53
> 5.0	47		47

Abbreviations: IDS, interval debulking surgery; SD, standard deviation.

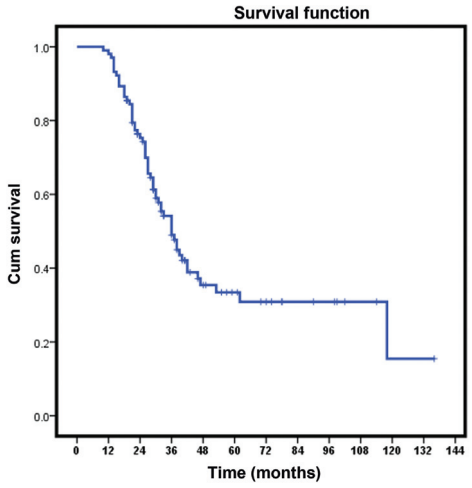

Fig. 1 Kaplan–Meier analysis of overall survival at 12, 36, and 60 months.

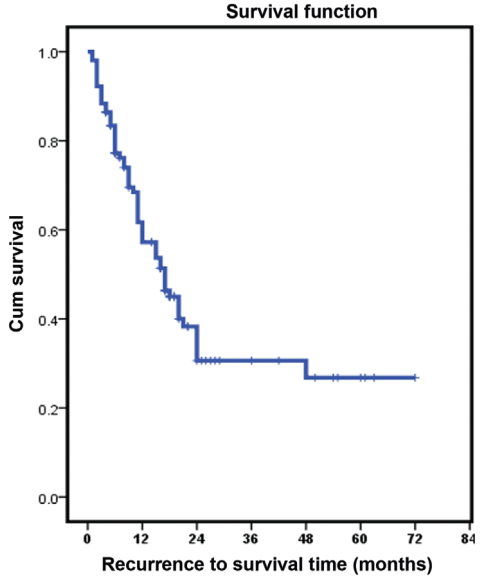

Fig. 2 Progression-free survival median was 17 months.

Based on binary logistic regression–univariate analysis, the factors predicting early recurrence are shown in ►**Table 5**. Among the various pretreatment and post-treatment factors, stage IV ovarian disease had the highest predictive value for recurrence (odds ratio [OR]: 12.2, 95% CI: 1.52–99.08, $p = 0.019$) followed by suboptimal resection R1 & R2 resection (OR: 8.8, 95% CI: 2.4–33, $p = 0.001$), high disease burden in omentum (CRS 1&2) (OR: 6.2, 95% CI: 1.08–16.58, $p = 0.002$), and platinum resistance (OR: 5.8, 95% CI: 2.3–10.67, $p < 0.001$).

Among the biochemical factors, a post-NACT serum Ca125 level > 45 and post-IDS serum Ca125 level > 35 IU/mL were significant predictors of early recurrence (OR: 5.8, 95% CI: 1.59–21.8, $p = 0.008$ and OR: 5.4, 95% CI: 2.3–12.73, $p < 0.001$) followed by pre-NACT neutrophil is to lymphocyte ration (NLR) (>11) and platelets is to lymphocyte ration (PLR) (>59). Other factors like residual disease in the ovary (OR: 3.268) and peritoneum (OR: 4.297) post-NACT at IDS also predicted an early recurrence. Post-NACT ascites had the lowest predictive value (OR: 1.4, 95% CI: 0.59–3.3, $p = 0.003$).

Discussion

This study included women with advanced stage high-grade EOC who were treated with three to four cycles of NACT followed by IDS and three or more cycles of adjuvant chemotherapy. The median age of our study population was 48 years, though majority of our cases were postmenopausal. Almost 90% cases were in stage IIIC, 95% women had ascites, 18% had distant metastasis to lymph nodes, 10% to lungs and 3% to liver. Thus, the advanced stage of the disease and unresectability at presentation were the reasons for

Table 5 Predictors of recurrence based on binary logistic regression–univariate analysis

Factors	Predictors of recurrence			
	OR	95% CI		
		Lower	Upper	*p*-value
Stage IV vs. stage III	12.279	1.52	99.08	0.019
R1 & R2 resection vs. R0	8.898	2.419	33.393	0.001
CRS 1 & 2 omentum	6.228	1.089	16.585	0.002
Platinum resistance	5.8	2.3	10.67	<0.001
POST_IDS Ca125 >35IU/ML	5.897	1.59	21.878	0.008
Post-NACT Serum Ca125> vs < 45IU/mL	5.432	2.316	12.738	<0.0001
CRS 1 peritoneum	4.297	1.042	5.063	0.038
CRS 1&2 ovary vs. CRS 3	3.268	0.107	4.674	0.005
Pre-NACT NLR_> vs < 11	3.2	1.428	7.171	0.004
Pre-NACT PLR >59	1.954	0.892	0.4283	0.093
Post-NACT ascites present vs. absent	1.417	0.595	3.375	0.003

Abbreviations: CI, confidence interval; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; OR, overall survival.

them undergoing IDS. The baseline characteristics in our study is in accordance with the literature except the age of onset, which is a decade younger as compared with the Western literature (European organisation for research and treatment of cancer [EORTC] and Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer [CHORUS] trials with a median age > 60 years).[8,9] However, similar age at presentation has been reported by most Indian studies like Maheshwari et al in 2018[10] and Baruah et al in 2015[11] (median age: 53 and 41 years, respectively). The exact reason for this age difference is not known; however, this could reflect the overall demographic profile of Indian population with a relatively younger population than the west or due to referral bias.

Ca125 has become well established as a tumor marker for EOC and has shown to have an important role in initial diagnosis, during therapy as a surrogate of clinical response and during follow-up. This study observed a markedly elevated baseline serum Ca125 level (median: 4,537 IU/mL) reflecting the advanced metastatic stage of the tumor. A similar profile of patients included in many studies has been reported by Vergote et al[8] (Ca125-1180, 15-41456), Faggotti et al[12]; SCORPION trial[12](Ca125-1579, 260-8792), Maheshwari et al[10] (Ca125 4294, 11-1,51,200), and Viswanath et al[13] (Ca125 median: 9385, with mean of 1808 ± 2205).

The major determinant of NACT response at IDS is the level of resection; complete resection or R0 or an optimum debulking surgery is the goal of IDS. In nearly 72% cases in this study, R0 resection was achieved. This is in accordance with various studies: Deo et al[14] and Batra et al[15] (R0 = 72% in each study) and one by Ghisoni et al[16] (R0 = 70%). The rates of optimal debulking surgery in the EORTC trial,[8] CHORUS,[9] JCOG,[17] SCORPION,[12] and Ghisoni et al[16] were 80, 73, 82, 90, and 70%, respectively.

The confirmation of chemo response can be demonstrated by the presence of specific pathological features by degree of tumor deposit and inflammation compared to fibrosis and necrosis stratified by a chemo response score.[18–21] In this study, only 10% of the removed specimen exhibited CR. In 90% cases, the disease was either present in the ovary (88%), omentum (72%), peritoneum (50%), or bowel /bladder (36%). Thus, the larger the tumor burden, more will be the non-responders and higher would be the risk of chemo-resistant clones. Various studies in the literature demonstrated the chemo-response score based on the histopathology of omental tumor burden with different criteria. This study used the criteria given by Bohm et al[22] who in their analysis of 71 omental specimen demonstrated no response (CRS1) in 5%, appreciable response (CRS 2) in 66%, and CR in 27%. Petrillo et al[21] evaluated 322 surgical specimen post-NACT, the criteria of response were CR (no residual tumor cells) in 7%, micro-PR (residual tumor foci < 3mm) in 32%, and macro-PR (residual tumor foci >3mm) in 61%.

The appropriate time interval from the completion of NACT to surgery (TTS) and from the end of NACT to start of adjuvant CT is still unknown. While general consensus supports avoiding unnecessary delays, studies regarding this are low and sparse. Clinical practice guidelines on the maximum time to surgery (TTS) and the results from numerous studies are conflicting. The commonly accepted practice is to perform surgery when neutropenia has resolved. Also, adjuvant CT should be started once the patient is adequately well-off postoperative period that usually occurs in 2 weeks time. In this study, the median TTS and time to postoperative chemo were 4 weeks each (range: 2–12 weeks and 2–10 weeks). The mean time interval between preoperative and postoperative chemotherapy was 7 weeks. Our results are consistent with the studies of Wang et al[23] who reported a

Table 6 Comparison with national and international studies

Name of the study	Mean age	Mean Ca125 at first presentation	R0 resection achieved post-NACT	5 years overall survival
EORTC trial[8]	>60 years	1180	80%	30 months
CHORUS study[9]	>60 years	–	73%	24 months
Maheshwari et al[10]	53 years	4294	–	–
Deo et al[14]	–	–	72%	–
Present study	47.8 years	3587	72%	36 months

cutoff time interval between preoperative and postoperative chemotherapy as 5 weeks (3 weeks NACT-IDS, 2 weeks); however, Lee et al[24] and Searle et al[25] reported this time interval as 6 and 9 weeks. One study by Chen et al[26] analyzed the TTS that was 4 weeks comparable to this study (4 weeks). Thus, as per the literature review generally accepted time interval from last platinum-based chemotherapy to IDS is 3 to 4 weeks (with neutrophils within normal range) that can extend to 8 weeks due to chemotherapy toxicities.

In this study, the median time to recurrence in the cohorts was 10 months with a mean of 15.3 months ranging from as early as 2 months to as late as 96 months. The shorter the TTR, the higher is the risk of platinum resistance. Shorter time to platinum-resistant recurrence (TTPR) for patients receiving NACT refers to the interval between the date of diagnosis and the date of first platinum-resistant recurrence is also an important measurement for chemosensitivity. Two retrospective studies presented differences in TTPR between patients receiving primary debulking surgery (PDS) and NACT-IDS. Petrillo et al[27] evaluated those patients with 175 stage IIIC and IV EOC in Italy135 were treated with NACT-IDS. A significantly shorter progression free interval (PFI) was observed in the NACT-IDS group; 13 months. This result was supported by da Costa et al 2015[28] who analyzed 237 patients with stage IIIC and IV EOC who underwent PDS or IDS at the AC Camargo Cancer Center from 2000 to 2013, and compared the TTPR between the groups. They revealed that the median TTPR was shorter for patients with NACT-IDS (39.3 vs. 80.2 months, $p = 0.012$). Multivariate analyses revealed that the hazard ratio of IDS was 1.92 ($p = 0.009$), which retained an increased risk of developing the platinum-resistant disease.

The OS at 5 years in our study was 34% with a median OS and progression-free survival (PFS) of 36 and 12 months, respectively. This is comparable to the survival figures quoted by other investigators using NACT (►Table 6). Those of EORTC, CHORUS[8,9] documented PFS and OS post-IDS as 12, 30 and 12, 24 months. The reason for a shorter PFS could also be explained on the grounds that a high tumor burden is seen at presentation and during IDS this may lead to persistence of microscopic disease that cannot be seen through naked eyes. Also, the emergence of resistant clones often makes the disease not amenable to adjuvant chemotherapy. However, the OS of 36 months in this study is comparable with others.

Conclusion

Ovarian cancer often presents at an advanced stage with NACT followed by IDS and then adjuvant CT is the standard treatment accepted in most centers around the world. The factors that have shown to influence the survival include Ca125 levels, NLR and PLR, presence of ascites, RECIST response criteria post-NACT, type of resection during IDS, and chemotherapy response score. Since the OS of advanced stage ovarian cancers is poor, further studies focusing on these factors can help us improve survival outcomes and modify treatment strategies for the same.

Conflict of Interest

None declared.

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