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A Prospective Observational Study of the Efficacy of Neoadjuvant Chemotherapy in Newly Diagnosed Inoperable Patients of Epithelial Ovarian Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Authors with affiliation 1 SJB, AVSS, SSN, PSD, AVV contributed for the subject management and content writing and accuracy. While author with affiliation 2 RS helped in the biostatistics and manuscript complication All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Ovarian cancer is the leading cause of death from gynecological cancers in developed countries. More than 70% of patients have Stage III – IV disease at diagnosis. The standard of care for advanced ovarian cancer is primary debulking surgery (PDS) followed by adjuvant (ADJ) chemotherapy. There are very few prospective randomized Indian studies that have evaluated the effectiveness of neoadjuvant chemotherapy (NACT) in advanced ovarian cancer. This study attempted to evaluate the efficacy of NACT in advanced epithelial ovarian cancer patients who were unfit for upfront surgery.

Methods: This was a prospective observational study involving newly diagnosed patients with inoperable epithelial ovarian cancer, conducted over a period of 18 months from October 2016 to March 2018 at the department of Medical Oncology at a tertiary care oncology center, situated in Hyderabad, India. Detailed clinical history, laboratory reports, imaging and histopathological reports were obtained and maintained in a standard proforma.

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Results: The median age at presentation was 51 years with a range of 37 to 70 years. 82.8% of the cases belonged to international federation of obstetrics and gynecology (FIGO) stage III. The objective response rate to NACT was 85.93% and the optimal cytoreduction rate was 85.96%. Post operative grade 3 or 4 adverse events were observed in 19.3% of the patients.
Conclusion: Neoadjuvant chemotherapy is an alternative approach to primary debulking surgery for advanced ovarian cancers. Among inoperable advanced epithelial ovarian cancer patients, neoadjuvant chemotherapy is associated with good objective response rates. Patients undergoing interval debulking surgery following neoadjuvant chemotherapy had less peri-operative morbidity and mortality.

Keywords: Epithelial ovarian cancer; neoadjuvant chemotherapy; optimal cytoreductive surgery; interval debulking surgery.

1. INTRODUCTION

Ovarian cancer is the leading cause of death from gynecological cancer in developed countries. Due to non specific symptoms, most patients are diagnosed in advanced stage [1]. More than 70% of patients have Stage III – IV disease at diagnosis. The standard of care for advanced ovarian cancer is primary debulking surgery (PDS) followed by adjuvant (ADJ) chemotherapy [2]. The primary goal of surgery is to achieve optimal cytoreduction, which is defined as residual tumor ≤1 cm after debulking surgery. Optimal cytoreduction has been found in many studies to be an important prognostic indicator [3]. There is an inverse correlation between survival and residual tumor after PDS [4]. Patients who achieved optimal cytoreduction were found to have better survival. Many studies illustrate that PDS is associated with high morbidity and mortality [5,6].

A significant proportion of patients with advanced disease have wide tumor dissemination which may require an extensive surgery to achieve optimal cytoreduction, thereby increasing the perioperative morbidity and mortality [7]. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and adjuvant chemotherapy is currently being proposed as an alternative approach, since it reduces the tumor burden rendering optimal cytoreduction feasible even in inoperable advanced stage disease.

Prospective randomized Indian studies evaluating the effectiveness of NACT in advanced ovarian cancer is limited. This is a prospective observational study which seeks to evaluate the efficacy of NACT in advanced epithelial ovarian cancer patients who are unfit for upfront surgery.

2. MATERIALS AND METHODS

This was a prospective study conducted over a period of 18 months from October 2016 to March 2018 at a tertiary care oncology center, situated in Hyderabad, India. Newly diagnosed patients with epithelial ovarian carcinoma, who were deemed inoperable, were included in this study. Patients with recurrence of ovarian cancer, deranged liver and renal functions or preexisting peripheral neuropathy were excluded. Sixty-four patients who fulfilled the eligibility criteria were included in this study. Detailed clinical history was taken and a standard proforma was maintained with details from patient's case records & investigation reports. Three cycles of neoadjuvant chemotherapy with Paclitaxel 175mg/m^2 and carboplatin, [Area under curve (AUC) – 5] were administered to the patients followed by re-evaluation with imaging. Patients with complete response, partial response or stable disease underwent interval debulking surgery. Optimal cytoreduction (OCR) was defined as the largest residual tumor nodule measuring 1 cm or less. Extended resections including gut resections were performed if it resulted in optimal surgical cytoreduction. Only retroperitoneal nodal sampling was done and no formal retroperitoneal lymph node dissection was performed. Relevant data was collected from the Radiology department and department of Pathology.

3. RESULTS AND DISCUSSION

The study involved patients aged between 37 and 70 years and the median age was 51 years. 27 patients (42.18%) had Eastern cooperative oncology group performance status (ECOG PS) of 0, 25 patients had ECOG PS 1 and 12 patients had ECOG PS 2. Among three patients (4.69%) with family history of ovarian cancer, two had an

affected 1st degree relative and one had an affected 2nd degree relative. BRCA 1 germline mutation was identified in one patient.

The duration of symptoms ranged from 1 to 8 months and the median duration was 3 months. 46 patients (71.87%) presented with abdominal pain, 40 (62.5%) had loss of appetite, 38 (59.37%) had abdominal distension, 18 (28.1%) had loss of weight and 6 (9.37%) had breathlessness. The hemoglobin of the patients ranged from 7.4g/dl to 12.2g/dl with a median value of 9.4g/dl.

The CA-125 levels ranged from 47.34U/ml to 38112.4U/ml and the median value was 867.5U/ml. Of the 64 patients, 4(6.3%) had FIGO stage IIIa, 8(12.5%) had stage IIIb, 41(64.1%) had stage IIIc and 11(17.2%) had stage IV. 82.8% cases belonged to stage III. Histopathology evaluation showed serous histology in 56(87.5%), clear cell histology in 2(3.1%), mucinous type in 1(1.6%), endometroid in 2(3.1%) and undifferentiated type in 3(4.7%).

In this study, 11 patients (17.2%) achieved complete response, 44 patients (68.8%) achieved partial response, 2 patients (3.1%) had stable disease and 7 patients (10.9%) developed progressive disease, as shown in Fig. 1. The Objective response rate (ORR) was 85.93%.

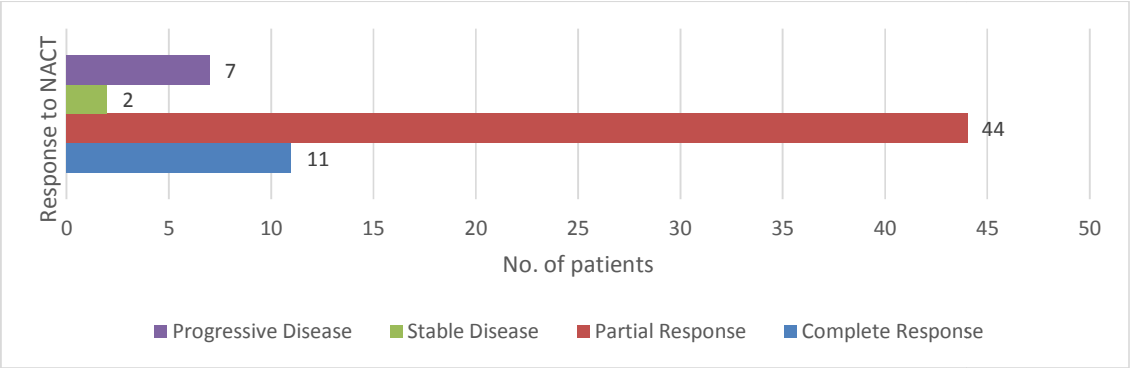

Fig. 1. Response to NACT

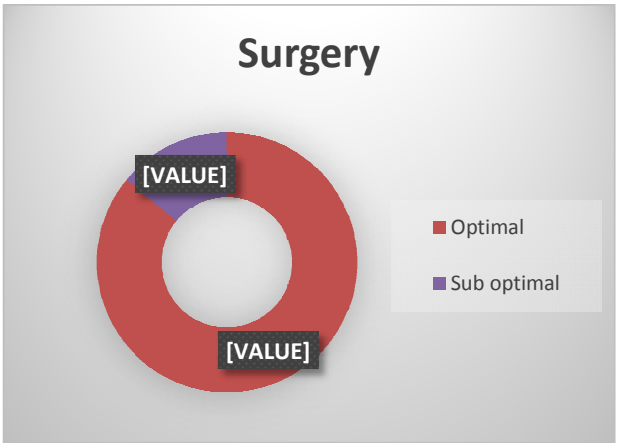

Fig. 2. Residual disease after IDS

Table 1. Residual disease after IDS

Residual disease in cm	No. of patients	% of operated patients
0	27	47.37
≤1	22	38.59
>1	8	14.04

Table 2. Stage-wise residual disease after IDS

Residual disease in cm	Stage III		Stage IV	
	No. of patients	%	No. of patients	%
0	25	51.02	2	25
≤1	20	40.82	2	25
>1	4	8.16	4	50

Overall optimal cytoreduction was achieved in 49 patients (85.96%), while the remaining 8 patients (14.04%) had suboptimal cytoreduction, as shown in Table.1. Among 49 stage III patients who underwent surgery, optimal cytoreduction was achieved in 45 patients (91.84%), while 4 patients (8.16%) had suboptimal cytoreduction. Among 8 stage IV patients who underwent surgery, optimal cytoreduction was achieved in 4 patients (50%) and the other 4 patients (50%) had suboptimal cytoreduction as shown in Table 2.

The time taken for interval debulking surgery ranged from 96 minutes to 150 minutes, the median time was 113 minutes. Blood loss during cytoreductive surgery ranged from 300ml to 450ml and the median value was 400ml. The duration of hospital-stay post-surgery ranged from 6 days to 15 days with a median duration of 8 days. Of the 57 patients who underwent interval debulking surgery, 5 patients (8.8%) required bowel resection, 3 patients (5.3%) required bladder repair and 19 patients (33.3%) required upper abdominal procedures in an attempt to achieve optimal cytoreduction.

Out of 57 patients who underwent surgery, 11 patients (19.3%) had post-operative grade 3/4 adverse events. 3 patients (5.3%) had hemorrhage, 3 (5.3%) had infection, 1 (1.8%) each had hypotension, gastrointestinal pain, vomiting, venous thromboembolism and vesico-vaginal fistula, as shown in Table 4. One patient (1.8%) expired on the 9th post-operative day. The interval between surgery and adjuvant chemotherapy ranged from 20 days to 37 days and the median duration was 24 days. The most common grade 3 or 4 chemotoxicity seen in this study was neutropenia followed by thrombocytopenia, anemia and hypotension. Grade 3/4 neutropenia was seen in 79.7% of patients. Febrile neutropenia was seen in 4.7% patients in this study. Grade 3 or 4 neuropathy was noted in 3.1% of patients.

3.1 Discussion

The median age at presentation was 51 years, as compared to western & Indian studies, which report a relatively higher median age (Anna fagotti et al – 65 years), a lower median age (UpsanaBaruah et al. – 41 years) respectively[7,8]. This was probably due to as yet unidentified environmental and genetic factors. The median hemoglobin level was 9.4g/dl , which is in agreement with most Indian studies (Upsana Baruah et al – 9.6 g/dl) [8,9].

82.8% cases belonged to FIGO stage III (82.8%), and is similar to other studies as shown in the Table 4 [1,7-10]. With respect to histology subtype, serous subtype was the most common subtype (87.5%), followed by undifferentiated histology (4.7%), while the EORTC NCIC trial had serous subtype in 58.1% and undifferentiated subtype in 26.9% [1].

This study had an objective response rate of 85.93% to NACT, compared to others, such as SCORPION trial, Anna Fagotti et al. (90.9%), Deo SVS et al (81.7%) and Upsana Baruah et al. (95.19%) [7-9]. The latter two were Indian studies. The ORR in this study was consistent with the high ORR seen in other studies as shown in the Table 5. This confirms the good efficacy of NACT in advanced epithelial ovarian carcinoma.

Table 3. Post-operative grade 3 or 4 adverse events

Post operative grade 3 or 4 adverse events	No. of patients	%
Hemorrhage	3	5.3
Infection	3	5.3
Hypotension	1	1.8
GI pain	1	1.8
Vomiting	1	1.8
VTE	1	1.8
VVF	1	1.8

Table 4. FIGO staging – comparison table [1,7-10]

Name of study	FIGO stage III	FIGO stage IV
Ignace Vergote et al.	75.7%	24.3%
Sean Kehoe et al.	92.7%	7.3%
Anna Fagotti et al.	75%	25%
Upsana Baruah et al.	84.6%	15.4%
Deo SVS et al.	72%	28%
Present study	82.8%	17.2%

Table 5. Response to NACT – comparison table

Name of study	Type of study	No. of patients receiving NACT	ORR(%)
Anna Fagotti et al.	Prospective	55	90.9
Deo SVS et al.	Retrospective	82	81.7
Upsana Baruah et al.	Retrospective	104	95.19
Present study	Prospective	64	85.93

Table 6. Optimal cytoreduction rate – comparison table

Name of study	Type of study	OCR (%)
Ignace Vergote et al.	Prospective	80.6
Sean Kehoe et al.	Prospective	73
Anna Fagotti et al.	Prospective	90.4
Upsana Baruah et al.	Retrospective	92.3
Deo SVS et al.	Retrospective	72
Lalitkumar et al.	Prospective	86.2
Shekar Sharma et al.	Retrospective	88.6
Present study	Prospective	85.96

The optimal cytoreduction rate (OCR) of 85.96% observed in this study was consistent with the high OCR reported by other studies - EORTC-NCIC trial (80.6%), SCORPION trial, Anna Fagotti et al. (90.4%) and UpsanaBaruah et al. (92.3%), [1,7,8] as shown in Table 6. This finding is in favor of NACT, since it was able to achieve OCR in most patients with advanced epithelial ovarian carcinoma. The median operation time noted in this study (113 minutes) is close to the median time of 120 minutes observed in the CHORUS trial [10]. The median blood loss was 398 ml, 35.1% received blood transfusion, mostly for the management of pre- existing anemia. The average blood loss reported by Upsana Baruah et al. was 350ml and 41.3% received blood transfusion [8].

The number of patients undergoing morbid surgical procedures like bowel resection and bladder resection in this study resembled those reported by Upsana Baruah et al. (8.8% vs 5.7% and 5.3% vs 3.84% respectively) [9] Upper abdominal procedures were done in 33.3% of patients in an attempt to achieve maximal cytoreduction, while Sean kehoe et al. reported 42.3% cases in the IDS arm and 100% in the PDS arm as requiring these [10]. Post-operative grade 3 or 4 adverse events were observed in 19.3% patients, which was consistent with the CHORUS trial (14% in the IDS arm vs 24% in the PDS arm). Hemorrhage (5.3%) and infection (5.3%) were the most common post operative grade 3 or 4 adverse events observed. The CHORUS trial also reported hemorrhage as the most common event, which was noted in 7% of patients [10].

The median hospital stay was less in the IDS arm (8 days), like in almost all other published studies (10 days in UpsanaBaruah et al) [8]. The median time for start of chemotherapy after IDS was 24 days which was similar to the SCORPION trial findings(27 days in the IDS arm Vs 40 days in the PDS arm) [10]. The post operative mortality rate in our study (1.8%) is comparable to those from the EORTC trial (0.7% in IDS arm Vs 2.5% in PDS arm), CHORUS trial (<1% in IDS arm Vs 6% in PDS arm) and SCORPION trial (0% in IDS arm Vs 3.6% in PDS arm) [1,7,10]. The mortality rate in IDS arm were unanimously lower compared to PDS arm across various published studies and ours.

Table 7. Chemotoxicity – comparison table

Grade 3 & 4 adverse events	J.K.Chan et al.	Present study
Anemia	15.9%	15.6%
Neutropenia	83.2%	79.7%
Febrile neutropenia	4.5%	4.7%
Thrombocytopenia	15.6%	17.2%
Hypotension	14.8%	10.9%
Nausea	3.2%	4.7%
Vomiting	4.2%	7.9%
Diarrhea	3.2%	3.1%
Neuropathy	2.8%	3.1%

The most common grade 3 or 4 chemotoxicity seen in this study was neutropenia followed by thrombocytopenia, anemia and hypotension. Febrile neutropenia was noted in 4.7%, while grade 3 or 4 neuropathy was seen in 3.1% of patients. These findings were comparable to the results of another study by J.K.Chan et al, [11] as shown in Table 7.

4. CONCLUSION

In patients with inoperable advanced epithelial ovarian cancer, NACT had an objective response rate that was comparable to other Indian and international studies. The objective response rate, optimal cytoreduction rate, chemotherapy toxicities observed in the current study was comparable to those reported across other Indian & internationally published literature. Patients receiving NACT had lower peri-operative morbidity and mortality. The overall findings were mostly consistent with those reported in the IDS arm. NACT is a promising approach in Indian patients with inoperable advanced epithelial ovarian cancer due to good objective response leading to increased rates of optimal cytoreduction with lower peri-operative morbidity and mortality.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943-53
2. Wright JD, Herzog TJ, Powell MA, et al. Morbidity of cytoreductive surgery in the elderly. Am J ObstetGynecol. 2004;190:1398-400.
3. Hoskins WJ, Mcguire WP, Brady MF, Homesley HD, Creasman WT, BermanM, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J ObstetGynecol. 1994;170:974-80.
4. Shekarsharma, Vijaykumar DK, Cjitrathara K, et al. Neoadjuvant chemotherapy in advanced epithelial ovarian cancer: A Retrospective study. Ind j med and pedia oncol. 2007;28(1):7-13.
5. Guidozzi F, Ball JH, et al. Extensive primary cytoreductive surgery for advanced epithelial ovarian cancer. GynecolOncol. 1994;53:326-30.
6. Shimada M, Kigawa J, Minagawa Y, Irie T, Takahashi M, Terakawa N, et al.

Significance of cytoreductive surgery including bowel resection for patients with advanced ovarian cancer. Am J ClinOncol. 1999;22:481-4.
7. Anna Fagotti, Gabriella Ferrandina, Giuseppe Vizzielli, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapyy in advanced epithelial ovarian cancer(SCORPION trial). Europen journal of cancer. 2016;59:22-33.
8. Upsana Baruah, Debabrata Barmon, Amal Chandra Kataki, et al. Neoadjuvant chemotherapy in advanced epithelial ovarian cancer: A survival study: Ind j of med. And pediaoncol. 2015;36(1):38-42.
9. Deo SVS, Goyal H, et al. Neoadjuvant chemotherapy followed by surgical cytoreduction in advanced ovarian cancer. Indian J Cancer. 2006;43(3):117-21.
10. Sean Kehoe, Jane Hook, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. Lancet Oncol. 2015;386: 249-257.
11. Chan JK, Brady MF, Penson RT, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. N Engl J Med. 2016;374(8):738-48.

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