

## Outcomes of advanced epithelial ovarian cancer with integration of metronomic chemotherapy: An Indian rural cancer centre experience

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### Abstract

**Background:** Paclitaxel-platinum and optimal cytoreductive surgery are the standard of care for ovarian carcinoma. Poor socioeconomic profile and therapeutic constraints in rural India poses a therapeutic challenge. **Aim:** To evaluate outcomes of epithelial ovarian carcinoma. **Objectives:** To calculate disease-free survival (DFS), overall survival (OS), and factors affecting outcomes. **Materials and Methods:** Data of patients diagnosed as ovarian carcinoma registered between March 2009 and March 2014 were retrieved. Demographic profile, chemotherapy and response, surgery, and disease progression were collected. Patients who underwent surgery or completed three cycles of chemotherapy were selected. Kaplan–Meir survival was used to determine disease-free and OS. Log-rank test used to evaluate factors affecting outcome. **Results:** Median follow-up is 26 months. 93/102 patients (91%) underwent cytoreductive surgery, of which 37 had primary cytoreduction (40%) while 56 had interval cytoreduction. 21/93 (23%), 57/93 (61%), and 15/93 (16%) patients were operated by local surgeons, surgeons of our hospital, and trained oncosurgeons, respectively. Induction paclitaxel-platinum was used in 35/63 (56%) patients while 28/63 patients (44%) received neoadjuvant metronomic chemotherapy. Median DFS and OS are 17 and 54 months respectively while 3 year OS of 66%. Median DFS of patients operated by oncosurgeons versus local surgeons were 22 months versus 15 months ( $P = 0.01$ ), OS was 54 versus 26 months ( $P = 0.01$ ). 40/88 (45%) patients received maintenance metronomic therapy after adjuvant chemotherapy with median of 6 months (range 2–18 months). Patients receiving metronomic maintenance had better DFS, 18 months versus 15 months ( $P = 0.69$ ). **Conclusion:** Induction therapy in ovarian carcinoma helps in selecting patients for cytoreductive surgery. Outcomes are better if operated by trained oncosurgeons. Maintenance metronomic has potential to delay disease progression.

**Key words:** Advanced epithelial carcinoma ovary, metronomic maintenance, metronomic neoadjuvant

### Introduction

Epithelial ovarian carcinoma is one of the leading causes of cancer-related mortality among Indian women. According to National Cancer Registry programme, the age-adjusted rate is 7.1 and 3.2 in urban and rural population-based registries per 100,000 population.<sup>[1,2]</sup> Ovarian carcinoma is third only to breast and cervical carcinoma in incidence among Indian women.<sup>[1]</sup> Paclitaxel-platinum doublet chemotherapy and optimal cytoreductive surgery are the standard of care for advanced epithelial ovarian carcinoma.<sup>[3]</sup> As most patients in rural India present with advanced stage with compromised nutritional and general condition management of such cancers becomes challenging in view of poor socioeconomic profile and therapeutic constraints.

### Materials and Methods

Case records of patients registered in our rural nodal cancer care center between March 2009 and March 2014 and diagnosed as epithelial ovarian cancer were retrieved. All patients who had even a single visit to oncology outpatient department were enrolled in database. Out of 117 such patients, 15 patients defaulted after the first visit and their whereabouts could not be traced hence excluded. Only patients who underwent surgery and/or received three cycles of chemotherapy and had posttherapy response evaluation were analyzed demographic profile including age, co-morbidities, stage, histology, baseline ascites, CA125, type of surgery (standard vs. substandard), timing of surgery (primary vs. interval), type of chemotherapy (intravenous vs. oral), timing of chemotherapy (neoadjuvant vs. adjuvant vs. metronomic maintenance), response to therapy (radiological vs. serological), disease progression and last follow-up status were recorded. Follow-up data were collected from case records, home

visits by social workers as well as telephonic conversation. This retrospective study was presented and approved by Institutional Review Board and Ethics Committee.

Patients were diagnosed with epithelial ovarian carcinoma if they presented with pelvic mass and had biopsy of serous or papillary adenocarcinoma. For mucinous histology, though history taking and examination followed by symptom-guided gastroscopy or colonoscopy was done if required. Patients presenting with ascites and had cytological evidence of adenocarcinoma with CA125/carcinoembryonic antigen (CEA) ratio more than 25 were treated as per epithelial ovarian carcinoma protocol. Majority of patients with pelvic mass along with ascites and omental deposits received neoadjuvant chemotherapy before cytoreductive surgery. Type of neoadjuvant therapy was decided as per the disease bulk, performance status and the cost of treatment. Either neoadjuvant intravenous chemotherapy paclitaxel 175 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (or carboplatin AUC 5) every 3 weekly or oral metronomic therapy with oral etoposide 50 mg BD, oral cyclophosphamide 50 mg BD both from D1 to D20 and tamoxifen 20 mg daily every monthly was used. Response evaluation computed tomography scan was done after three cycles of neoadjuvant chemotherapy or 3 months of neoadjuvant metronomic chemotherapy along with CA125. After surgery patients underwent adjuvant intravenous chemotherapy to complete six cycles or adjuvant metronomic therapy for 6 months. Patients who had disease control after completion of adjuvant therapy came for regular follow-up and gave consent were offered to take low dose oral metronomic maintenance therapy for maximum of 18 months.

Cytoreductive surgery was done at different time points by various surgical disciplinarians such as gynecologists, general surgeons,

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trained oncosurgeons, and gynecologic oncologist. Standard surgery was defined as total abdomen hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Any surgery less than that described under standard surgery was termed as substandard surgery. Radiological response evaluation of measurable lesion was done by RECIST criteria (version 1.1), and overall best response was assessed by Gynecological Cancer Intergroup criteria. Disease-free survival (DFS) was defined as time interval from date of first induction chemotherapy till date of relapse or death from any cause. Overall survival (OS) was defined as time interval from date of first induction chemotherapy till death from any cause. Median follow-up was calculated from date of diagnosis to date of last follow-up. All statistical analysis was carried out using SPSS software version 16 SPSS Inc. Released 2007.SPSS for Windows, Chicago, SPSS Inc. Kaplan–Meir curve was plotted for DFS and OS in months. Log-rank test was used to compare the DFS and OS in different groups.

### Results

Between March 2009 and March 2014, total 117 patients were registered as epithelial ovarian carcinoma in our hospital. Out of these 15 patients defaulted after the first visit, hence excluded for analysis. Ninety-three out of 102 patients (91%) underwent cytoreductive surgery; of which 36 had primary cytoreductive surgery (40%) while remaining 56 had interval cytoreductive surgery. Forty-seven patients (51%) underwent standard surgery while remaining 46 patients (49%) has substandard surgery. About 44% (20/46) of patients who underwent suboptimal surgery were those done by local primary general surgeons and gynecologist in which primary resection was attempted in advanced bulky disease without downstaging with neoadjuvant chemotherapy. Only 3/46 (6%) patients underwent suboptimal surgery since 2013. 21/93 (23%), 57/93 (61%), and 15/93 (16%) patients were operated by local surgeons, surgeons of our hospital and trained oncosurgeons, respectively. Eighty-one patients (80%) had stage III while 10 patients had stage IV (12%) epithelial ovarian cancer, while remaining patients were stage I (10 patients) and stage II (1 patient) [Table 1].

At baseline on biopsy, 24 patients had serous adenocarcinoma, 16 patients had papillary adenocarcinoma, 2 patients had endometrioid adenocarcinoma while 3 had mucinous adenocarcinoma of ovary. Therapeutic ascitic cytology yields metastatic adenocarcinoma in 57 patients with raised CA125/CEA ratio. Among patients receiving adjuvant intravenous chemotherapy, 13/63 (20%) received cyclophosphamide cisplatin for six cycles while remaining 50 patients (80%) received six cycles of paclitaxel-platin doublet. Induction paclitaxel-platinum doublet was used in 35/63 (56%) patients while 28/63 patients (44%) received neoadjuvant oral metronomic chemotherapy. 56/63 (89%) patients who received neoadjuvant therapy underwent cytoreductive surgery. 5/56 (9%) patients had a pathological complete response of which 4 (80%) patients had received induction paclitaxel-platinum chemotherapy.

Median follow-up is 26 months. Median DFS and OS are 17 and 54 months respectively while 3 year survival of 66% [Figures 1 and 2]. Primary cytoreductive surgery had an inferior trend to disease-free interval (15 months) compared to those who had interval cytoreduction (19 months,  $P = 0.58$ ). Median DFS of patients operated by oncosurgeons versus local surgeons were 22 months versus 15 months respectively ( $P = 0.01$ ) while comparison among

them for OS was 54 versus 26 months ( $P = 0.01$ ). 40/88 (45%) patients received maintenance metronomic therapy after adjuvant chemotherapy with median of 6 months (range 2–18 months). Patients receiving metronomic maintenance had better trend to DFS, 18 months versus 15 months ( $P = 0.69$ ). There was no statistically significant difference in outcome irrespective of age, histology, timing of surgery, type of chemotherapy, response to chemotherapy, and type of neoadjuvant therapy [Table 2].

### Discussion

The evolution of therapy over a couple of decades have revolutionized the management of advanced epithelial ovarian carcinoma. The superiority of paclitaxel instead of cyclophosphamide along with cisplatin as adjuvant therapy was followed by noninferiority of carboplatin with respect to cisplatin with improved toxicity profile.<sup>[4,5]</sup> Thus, paclitaxel and carboplatin became the standard of care in the management of epithelial ovarian carcinoma. In bulky and advanced disease equivalent outcomes can be achieved with neoadjuvant chemotherapy followed by interval cytoreductive surgery compared to primary cytoreduction followed by adjuvant therapy.<sup>[6]</sup>

Our hospital is a rural model cancer control center situated in one of the most socioeconomically backward region of modern



Figure 1: (a1 and a2) Neoadjuvant oral metronomic chemotherapy only with partial response after 3 months in a patient with locally advanced epithelial carcinoma ovary. (b1 and b2) Neoadjuvant paclitaxel – cisplatin with partial response after three cycles of intravenous chemotherapy

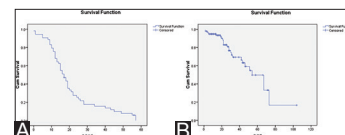


Figure 2: Panel A shows the graph for DFS while Panel B shows the graph for OS

Table 1: Demographic details

Profile	Distribution	Numbers (%) (n=102)
Age (years) median=55	<60	75 (74)
	>60	27 (26)
Co-morbidities (any)	Yes	19 (19)
	No	84 (82)
Ascites	Yes	61 (60)
	No	41 (40)
Baseline CA125 (U/ml)	<480	52 (51)
	>480	50 (49)
Timing of surgery (n=93)	Primary	37 (36)
	Interval	56 (55)
Stage at presentation	III	81 (80)
	IV	10 (9.5)
Histology	I and II	11 (10.5)
	Papillary	16 (16)
Histology	Serous	24 (23)
	Mucinous	3 (3)
	Endometrioid	2 (2)
	Cytological adenocarcinoma	57 (56)

**Table 2: Factors affecting progression free survival**

Factors	Strata	PFS	P value
Age (years)	<60	17	0.55
	>60	15	
Co-morbidities (any)	Yes	15	0.06
	No	18	
Ascites	Yes	16	0.17
	No	17	
Baseline CA125 (U/ml)	<480	18	0.09
	>480	16	
Timing of surgery (n=93)	Primary	15	0.58
	Interval	19	
Stage at presentation	III	16	0.55
	IV	13	
Adjuvant chemo	Pac-cis*	16	0.14
	Cyc-cis <sup>#</sup>	15	

\*Paclitaxel- platinum <sup>#</sup>cyclophosphamide-cisplatin

India.<sup>[7]</sup> Majority of resident population are dependent on agriculture as the source of income, and considerable number of them are landless laborers.<sup>[7]</sup> More than 40% of the population lie below poverty line with per capita income of <8000 Rs./year with negative growth rate.<sup>[8]</sup> Lack of awareness and sociofamilial neglect often result in patients presenting with advanced disease with no means to avail standard therapy which further constraints already scarce economic resource. Moreover, being a distant rural district delivering individualized expert consult with best of medical and surgical specialties is an uphill challenging task.

Metronomic chemotherapy is the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug-free breaks.<sup>[9]</sup> The success of metronomic therapy is currently believed to rely on three main mechanisms: Continuous administration, activation of cancer immunology, and antiangiogenic effects.<sup>[9-11]</sup> Among studies in ovarian carcinoma, majority of studies using metronomic therapy have used in either relapsed/refractory ovarian carcinoma or in combination with standard chemotherapy to improve outcomes due to antiangiogenic effect with minimal toxicity.<sup>[11-14]</sup> As the cost of metronomic therapy is <16\$/month compared to a single cycle of standard paclitaxel carboplatin doublet (300\$) with demonstrated benefit, we started the use of metronomic oral chemotherapy first in relapsed/refractory ovarian carcinoma followed by maintenance therapy after definitive treatment and finally as neoadjuvant therapy in nonaffording patients with poor tolerance to standard platin doublet.

We report outcomes of patients with epithelial ovarian carcinoma treated at our institute between March 2009 and March 2014. With median follow-up of 26 months, median DFS and OS are 17 and 54 months, respectively. Compared to outcomes reported in Western literature with DFS between 18 and 19 months and OS ranging between 38 and 59 months with standard paclitaxel-platinum doublet, our attempts to manage epithelial ovarian carcinoma with the introduction of metronomic therapy either as maintenance, adjuvant, or neoadjuvant therapy have resulted in similar outcomes. Significant improvement in disease-free and OS of patients operated by oncosurgeons compared with general surgeons is the proof of principle that quality and extent of surgery favorably impacts the outcome.<sup>[15-17]</sup> Maintenance metronomic therapy was received by 45% of patients who completed adjuvant therapy and were on regular follow-up with median duration of 6 months. Patients receiving metronomic maintenance had better trend to DFS, 18 months versus 15 months ( $P = 0.69$ ).

Being retrospective, we do not rule out any selection bias and inadvertent omission of patients which might have inflated the outcome. Only patients whose case records were found were eventually entered in our database and analyzed which might not have included all patients with epithelial ovarian carcinoma treated or referred in our institute. Due to lack of meticulous recording of toxicities, we could not report detailed toxicity profile of patients receiving standard combination intravenous chemotherapy or metronomic therapy. Similarly, due to lack of stringent reporting by an operating surgeon total number of patients who underwent R0/optimal resection could not be ascertained, which we know has direct prognostic implications.<sup>[18,19]</sup> About 49% patients had substandard surgery with 44% of them done by local surgeons and gynecologists shows lack of awareness regarding benefit of downstaging with use of neoadjuvant chemotherapy in advanced and bulky disease among community specialties. However, with gain in expertise, technical skills, and availability of trained oncosurgeons and gynecologic oncologist the number of substandard surgery reduced to <6% since 2013.

Poor socioeconomic condition with delayed presentation and advanced disease in rural India poses a significant challenge for health care providers to give standard accepted treatment in such resource constraint setting. Induction therapy in advanced bulky epithelial ovarian carcinoma helps in selecting patients for cytoreductive surgery, however, this need to be emphasized among community practitioners so that prompt referral to higher center is initiated. Outcomes of epithelial ovarian carcinoma are better if operated by trained oncosurgeons compared to general surgeons. Maintenance metronomic chemotherapy beyond adjuvant therapy has potential to delay disease progression and when used as neoadjuvant therapy does induce significant responses. However, this needs to be evaluated in prospective randomized study for its possible merit before making any recommendation.

## Conclusion

Induction therapy in ovarian carcinoma helps in selecting patients for cytoreductive surgery. Outcomes are better if operated by trained oncosurgeons. Maintenance metronomic has potential to delay disease progression.

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## Conflicts of interest

There are no conflicts of interest.

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