

Patterns of Treatment and Outcomes in Epithelial Ovarian Cancer: A Retrospective North Indian Single-Institution Experience

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PURPOSE Ovarian cancer (OC) is ranked as the third most common gynecologic cancer in various Indian cancer registries. In India, OC is seen in the younger age group, with a median age < 55 years being reported by most of the studies. The majority of patients are diagnosed in advanced stage (70%-80%), where the long-term (10-year) survival rate is poor, estimated at 15%-30%. The aim of this study was to evaluate clinical epidemiology, treatment patterns, and survival outcomes in patients with epithelial OC.

METHODS This was a retrospective analysis of patients with epithelial OC who were treated at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, over a period of 9 years, from January 2010 to December 2018.

RESULTS OC constituted 2.94% of all cancers registered. Epithelial OC constituted 88.4% of all OCs, with a median age 50 years. More than two third of patients belonged to rural background and the majority (76.9%) of the patients were in stage III or IV at the time of diagnosis. The main presenting symptoms were abdominal distension/bloating (46.5%) and gastrointestinal disturbances (35.2%). The most common histologic types were serous (65.9%) followed by mucinous carcinoma (15%). Median overall survival for the whole study cohort was 30 months (95% CI, 28.0 to 31.9). Median overall survival for stage I, II, III, and IV was 72, 60, 30, and 20 months, respectively.

CONCLUSION Most of the patients presented in advanced stage of the disease and have poor outcome. Delay in diagnosis and improper management before registering in tertiary cancer center and lack of tertiary care facilities are the root causes of poor outcomes. The general population and primary care physicians need to be made aware of OC symptoms.

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INTRODUCTION

In females, ovarian cancer (OC) is the 8th most common incident cancer and ranks eighth in cancer-related deaths globally.¹ According to GLOBOCAN 2020 statistics, 1.6% of new cases and 2.1% of deaths of all sites are attributable to OC.¹ In India, data collected from 27 population-based cancer registries between 2012 and 2014 registered 4,818 incident cases of OC, with huge regional variation across the country (688 cases in Delhi to 15 cases in Nagaland), with a mean age-adjusted rate of 5.3 per 100,000 women. In most of these registries, OC ranked third.² In Western patient cohorts, the median age of diagnosis of OC is 63 years,^{3,4} whereas in India, the median age of diagnosis has been reported to be < 50 years in most of the studies.^{5,6} The majority of the patients are diagnosed in advanced stage (70%-80%), with poor long-term survival (15%-30%), compared with those with early-stage disease, where survival exceeds 80%.^{2,3} Surgery and systemic therapy form the backbone of treatment in these patients. The goal of surgery is to

accurately stage the disease in patients with early disease (staging laparotomy) and to debulk the tumor in advanced cases to an optimal residual level (optimal cytoreduction). The sequence of these modalities is determined by the stage of the disease and the performance status of patient. In India, treatment outcomes in these patients are still inferior to their Western counterparts.^{1,5,6}

There has been a significant improvement in the treatment landscape of OC in the past few decades, leading to improvement in outcomes. Incorporation of hyperthermic intraperitoneal chemotherapy and novel systemic agents such as antiangiogenic drugs and poly (ADP-ribose) polymerase (PARP) inhibitors has shown benefit in a number of phase III trials.⁷ However, because of logistic and resource constraints, there has been variable acceptance of these advancements globally, and especially in low-income countries and low-and middle-income countries, where the variations are even more diverse because of financial and training constraints.^{7,8} The real-world

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CONTEXT

Key Objective

To evaluate clinical epidemiology, treatment patterns, and survival outcomes in patients with epithelial ovarian cancer (OC).

Knowledge Generated

We had a younger cohort of patients with median age 50 years (range, 18-85 years), with the majority belonging to rural background and poor social economic stratum. The majority of our patients (three fourth) presented with advanced stage of disease (stage III and IV). More than 70% of patients were operated by surgical/gynecologic oncologist, and optimal debulking was achieved in 62% of patients. Lower stage of disease, optimal cytoreduction, expertise of operating surgeon, and upfront surgery were associated with significantly improved survival.

Relevance

This study will provide us a strong evidence to base our practice of sequencing of surgery and chemotherapy in the management of OC and guide us to form locally relevant protocols for early detection and optimal management of OC in our population.

data depicting the impact of these advancements in India are available in the form of few single-institution studies from few major centers of the country.^{5,6,9} Our cancer center is constituted of a team of well-trained surgical and medical oncologists who comprehensively manage OC, which is true with most of the tertiary care centers in the country. This is the first study from Kashmir to evaluate clinical and demographic profile, treatment patterns, and survival outcomes in patients with epithelial ovarian cancer (EOC).

METHODS

This is a retrospective analysis of patients diagnosed with EOC (including primary peritoneal carcinomatosis and fallopian tube cancer), treated at the state cancer institute of Sher-i-Kashmir Institute of Medical Sciences located in Jammu and Kashmir, India. Patients treated over a period of 9 years, from January 2010 to December 2018, were included in the study. Data were retrieved from a prospectively maintained database of the state cancer institute after formal approval from the institutional ethics committee (IEC). Data related to patients' demography, clinical status, pretreatment staging, treatment (including surgical details), and follow-up data were abstracted. Patients with incomplete data and nonepithelial histology were excluded.

Data Analysis

The data were first keyed into a Microsoft Excel spreadsheet and cleaned for any inaccuracies. Statistical analysis was done using IBM SPSS Statistics for Windows from IBM Corp (released 2020, Version 27.0. Armonk, NY). Categorical variables were shown in the form of frequencies and percentages. Survival was calculated using the Kaplan-Meier method, and the groups were compared using log-rank test. Progression-free survival (PFS) was estimated from the time of diagnosis to the time of progression or death, whereas overall survival (OS) was calculated from the time of diagnosis to death due to any cause. Patients not experiencing any event were censored at the time of last follow-up. Continuous variables were compared using

Mann-Whitney U test. Univariate and multivariate Cox regression analysis was done to study the effect of covariates on survival. Analysis was also done to assess the impact of sidedness of ovarian tumor (unilateral v bilateral) on survival.

Ethics

The procedure in conducting the study was as per the IEC guidelines and as per the Helsinki Declaration of 1964, revised in 2013. This study was approved by the IEC under the IEC SKIMS protocol number RP-17/2019 dated February 16, 2019. Informed consent was waived, as this was a retrospective audit of the health records.

RESULTS

A total of 34,614 cases of cancer were registered during the study period (January 2010-December 2018), of which 1,019 patients (2.94%) were registered with diagnosis of OC. EOC was confirmed in 663 patients (65%) and data related to these patients were analyzed.

The clinicodemographic profile of patients is tabulated in [Table 1](#). The median age of our patient cohort was 50 years (range, 18-85 years). Most of the patients belonged to rural background, and the majority belonged to the below poverty line socioeconomic stratum. Most of the patients were multiparous, and almost half of them were premenopausal. The majority of the patients presented either with abdominal bloating (because of ascites) or gastrointestinal disturbances, and most of them presented with good performance status. More than three fourth of the patients presented with advanced disease (stage III or IV), and the majority of them had serous histology. The baseline serum cancer antigen-125 level was elevated in 79.8% of patients.

Of the 663 patients, staging laparotomy was performed in 23% (n = 152), primary cytoreduction in 30.1% (n = 200), interval cytoreduction in 34.7% patients (n = 230), and palliative chemotherapy only in 81 patients (12.2%; [Table 2](#)). More than 70% of patients were operated

TABLE 1. Demographic and Clinical Characteristics of Patients

Characteristics	Frequency (n = 663)
Age, years	
Mean (SD)	50 (± 12.85)
Median (SD)	50 (± 13.01)
Range	18-85
Regional distribution, No. (%)	
Rural	462 (69.6)
Urban	201 (30.3)
Charlson comorbidity index, No. (%)	
0	337 (56.8)
≥ 1	326 (49.1)
Menopausal status, No. (%)	
Premenopausal	374 (56.4)
Postmenopausal	289 (43.6)
Contraception use, No. (%)	
Present	86 (12.9)
Absent	577 (87.1)
History of smoking, No. (%)	
Present	22 (3.3)
Absent	641 (96.7)
Parity, No. (%)	
Nulliparous	11 (1.65)
Uniparous	42 (6.3)
Multiparous	610 (92.05)
Family history of malignancy, No. (%)	
Present	23 (3.46)
Absent	640 (96.5)
Symptom distribution, No. (%)	
Abdominal distension/bloating	308 (46.5)
GI disturbances	234 (35.2)
Abdominal pain	139 (21.1)
Menstrual disturbances	57 (8.6)
Others	160 (24.1)
Symptoms duration, No. (%)	
Up to 2 months	95 (14.3)
2-4 months	211 (31.8)
> 4 months	357 (53.8)
Performance status (ECOG), No. (%)	
≤ 1	474 (71.4)
≥ 2	189 (28.5)
Histology	
Serous	437 (65.9)
Mucinous	100 (15)
Endometrioid	66 (9.9)
Clear cell	49 (7.3)
Others	11 (1.65)

(Continued in next column)

TABLE 1. Demographic and Clinical Characteristics of Patients

(Continued)

Characteristics	Frequency (n = 663)
Serum CA-125 at diagnosis, U/mL, No. (%)	
< 35	134 (20.2)
> 35	529 (79.8)
Stage at diagnosis, No. (%)	
I	34 (5.1)
II	118 (17.7)
III	336 (50.67)
IV	175 (26.3)

Abbreviations: CA-125, cancer antigen-125; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

by surgical/gynecologic oncologist, and optimal debulking was achieved in 62% (267/430) of patients. Optimal cytoreduction rate was higher (83% v 64.7%) in favor of interval cytoreduction. Although the majority of women responded to platinum doublet chemotherapy, 11.2% of women (n = 35) received second-line chemotherapy because of suboptimal response. In first relapse, 50.9% of patients had platinum-sensitive disease. The majority of platinum-sensitive patients were rechallenged with platinum doublet either with paclitaxel/carboplatin or liposomal doxorubicin/carboplatin. Women with platinum-resistant relapse were treated with

TABLE 2. Treatment Details of Patients

Treatment History	Frequency (%)
Intent of treatment at diagnosis	
Curative	582 (87.8)
Palliative	81 (12.2)
Primary treatment in the curative group (n = 582)	
Staging laparotomy	152 (26.1)
Primary debulking surgery	200 (34.4)
Interval debulking surgery	230 (39.5)
Operating surgeon (n = 582)	
Oncosurgeon	416 (71.4)
Gynecologist/general surgeon	166 (28.5)
Extent of debulking in advanced stage (n = 430)	
Optimal cytoreduction	267 (62.1)
Suboptimal cytoreduction	163 (37.9)
Chemotherapy response (n = 311)	
Complete response	90 (28.9)
Partial response	155 (49.8)
Stable disease	31 (9.9)
Progressive disease	35 (11.2)
Platinum-free interval (n = 557)	
Platinum-resistant	273 (49.1)
Platinum-sensitive	284 (50.9)

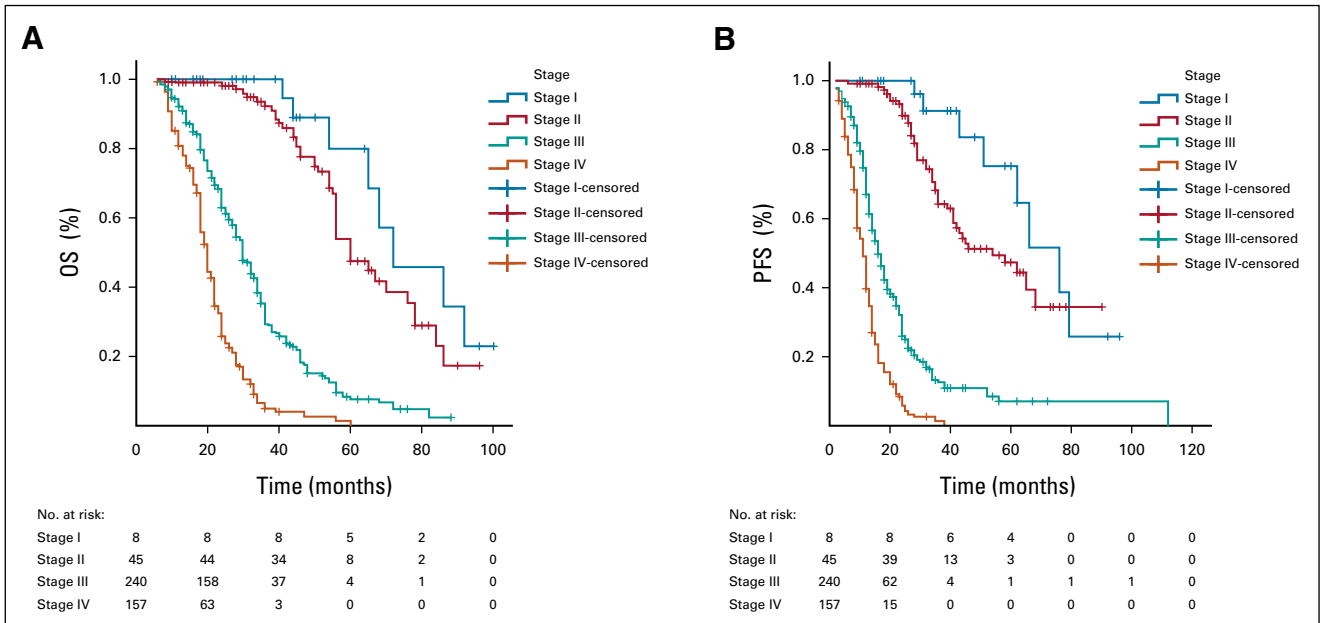


FIG 1. (A) Kaplan-Meier plot of OS (months) in relation to stage. (B) Kaplan-Meier plot of PFS in months for different stages. OS, overall survival; PFS, progression-free survival.

second-line chemotherapy, most commonly with liposomal doxorubicin, gemcitabine, or topotecan.

The median duration of follow-up was 25.7 months (standard deviation ± 8.63). The median OS for the whole study cohort was 30 months (95% CI, 28.0 to 31.9), whereas the corresponding median PFS was 18 months (95% CI, 16.0 to 20.0). Median OS for stage I, II, III, and IV was 72, 60, 30, and 20 months, respectively (Fig 1A), and their

corresponding median PFS was 70, 54, 16, and 11 months (Fig 1B). The patients who underwent optimal cytoreduction had significantly improved OS compared with those who underwent suboptimal surgery (36 months [95% CI, 33.2 to 38.7] v 28 [95% CI, 24.8 to 31.1] months, $P < .001$; Fig 2). Similarly, patients who had been operated by a surgical oncologist or gynecologic oncologist had significantly improved OS compared with patients who had been operated

FIG 2. Kaplan-Meier plot depicting OS (months) in relation to extent of surgery. OS, overall survival.

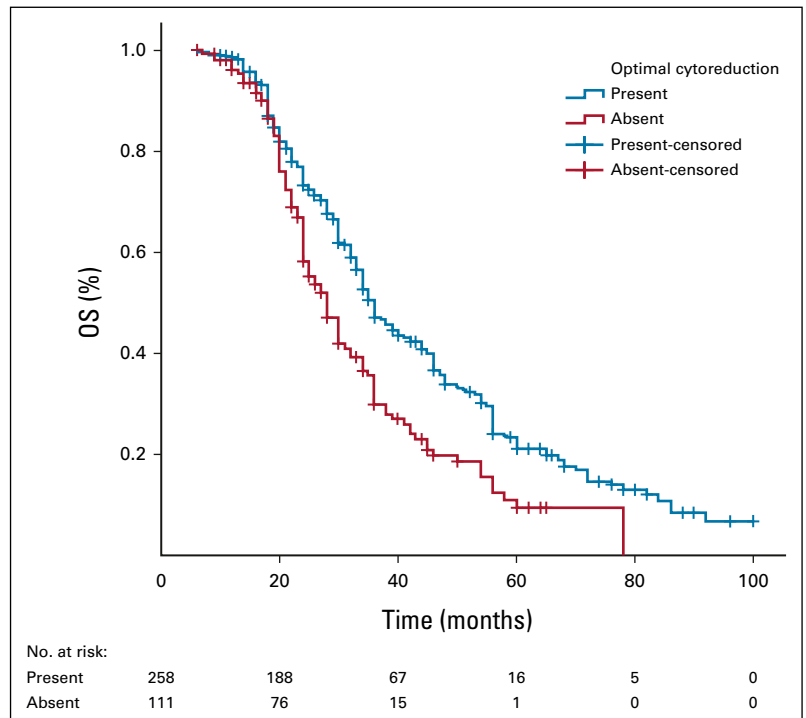
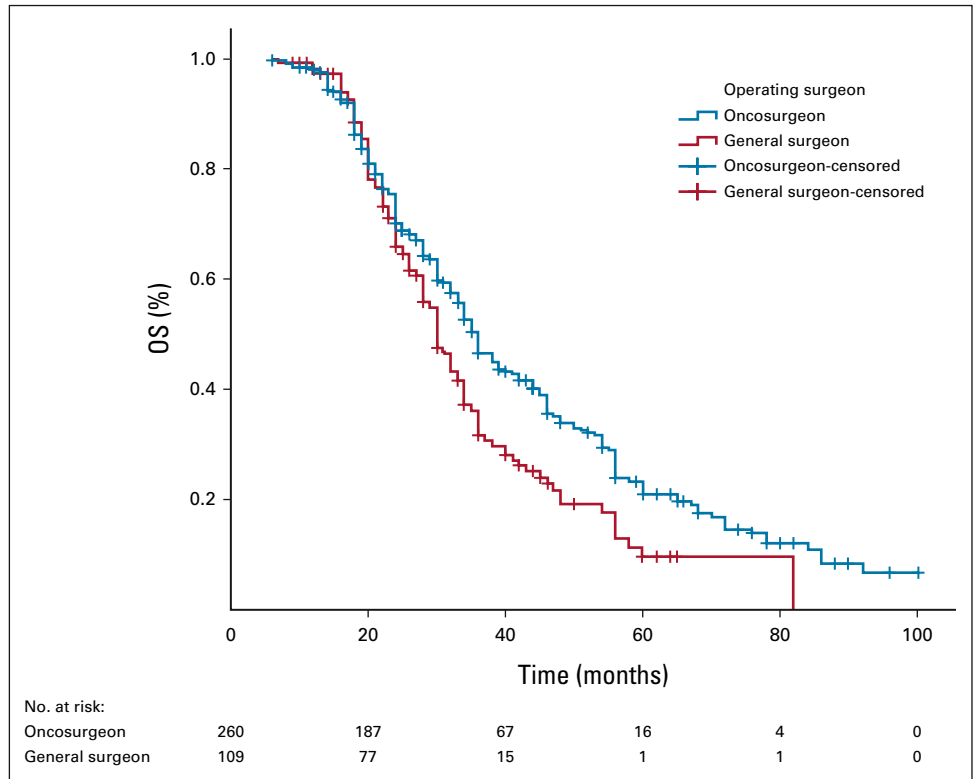


FIG 3. Kaplan-Meier plot depicting OS in terms of surgeon expertise. OS, overall survival.



by a gynecologist or general surgeon (36 [95% CI, 33.3 to 38.6] v 30 [95% CI, 27.2 to 32.7] months, $P < .001$; Fig 3). An improvement in OS was noted in patients undergoing upfront debulking compared with interval cytoreduction (44

[95% CI, 39.5 to 48.5] v 29 months [95% CI, 26.5 to 31.5], $P < .001$; Fig 4). Platinum-sensitive relapse patients showed significantly improved OS compared with platinum-resistant patients. The median OS for platinum-free interval < 3, 3-6,

FIG 4. Kaplan-Meier plot depicting OS in relation with treatment approach. f/b, followed by; NAct, neoadjuvant chemotherapy; OS, overall survival; Sx, surgery.

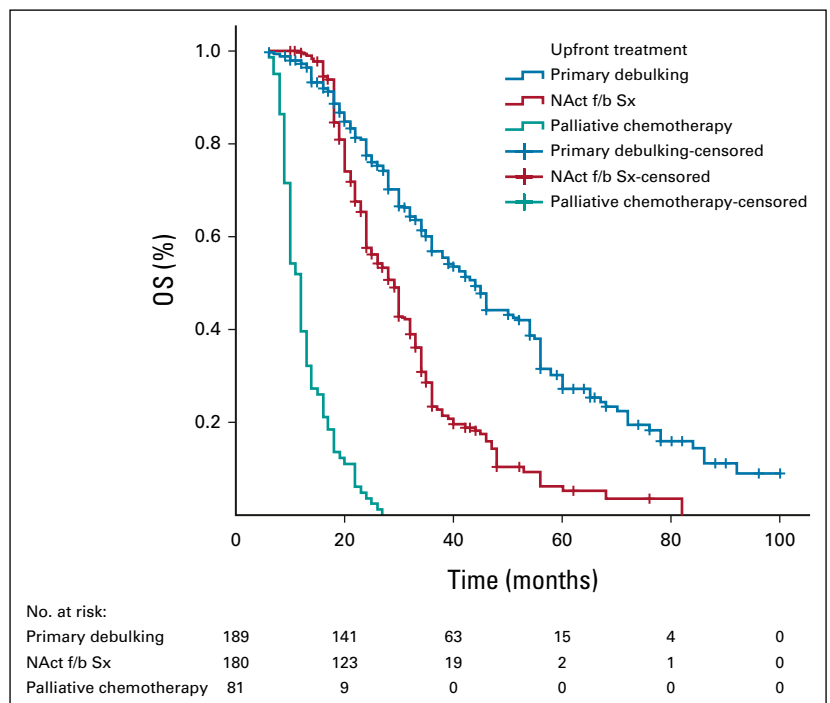


TABLE 3. Univariate Analysis

Characteristic	HR	Lower CI	Upper CI	P
Stage				
IV	Ref	—	—	—
I	0.050	0.024	0.104	< .001
II	0.084	0.059	0.120	< .001
III	0.382	0.310	0.472	< .001
Optimal cytoreduction				
No	Ref	—	—	—
Yes	0.633	0.505	0.793	< .001
Operating surgeon				
General surgeon	Ref	—	—	—
Oncosurgeon	0.719	0.573	0.902	.004
Upfront treatment				
Neoadjuvant chemotherapy	Ref	—	—	—
Primary debulking	0.456	0.368	0.564	< .001

Abbreviation: HR, hazard ratio.

7-12, and > 12 months was 14, 18, 30, and 56 months, respectively.

On univariate analysis, lower stage of disease, optimal cytoreduction, the expertise of operating surgeon, and upfront surgery were all associated with significantly favorable survival (Table 3). However, on multivariate analysis, only stage and optimal cytoreduction showed significant correlation with survival (Table 4). The location of tumor (unilateral v bilateral) also showed no significant impact on OS and PFS.

DISCUSSION

OC ranks among the top 10 most common malignancies in international and national cancer registries.^{1,2} Epithelial histology is proportionately predominant,⁴ and most of the patients with malignant epithelial tumors present with advanced stage, with associated poor outcomes.^{10,11} This is a retrospective analysis of patients treated for EOC at a tertiary care center in North India between January 2010 and December 2018, and, to our knowledge, is the first report from Kashmir to audit the patterns of treatment and outcomes in these patients.

TABLE 4. Multivariate Cox Regression

Characteristic	HR	95.0% CI for Exp(B)		P
		Lower	Upper	
Stage	3.015	2.484	3.660	< .001
Optimal cytoreduction	0.537	0.408	0.705	< .001
Operating surgeon	1.070	0.827	1.385	> .05
Upfront treatment	1.001	0.745	1.344	> .05

Abbreviation: HR, hazard ratio.

About 76% of our patients presented with advanced stage of disease (stage III-IV), similar to the findings reported in other Indian studies.^{12,13} Lack of proper screening tests, delayed referral by primary care physician, and chronic symptoms mimicking other common ailments are reasons for late stage of presentation in these patients.¹⁴

The most frequent histologic subtype was the serous type, followed by mucinous and endometrioid types, similar to other studies.^{13,15} It has been observed that patients with OCs may have symptoms for several months before their diagnosis.¹⁶⁻¹⁸ In this study, we observed that abdominal distension and gastrointestinal disturbances were the most frequent symptoms. Symptom duration was more than 4 months in 53.8% of patients, followed by 2-4 months in 31.8% of patients. Similar findings were observed in other Indian studies too.^{5,13,16}

Complete resection of the macroscopic disease is one of the most important independent prognostic factors in advanced OC.^{10,11,19} Our study also corroborated the same findings (36 months v 28 months in favor of optimal cytoreduction, $P < .001$; Fig 2). Surgical expertise has a strong bearing on the ability to achieve optimal cytoreduction in OC, with the surgeons having trained in gynecologic oncology faring better than others.²⁰⁻²⁵ Data from our study confirmed the same, with those patients operated by surgical oncologists or gynecologic oncologists having significantly improved median OS compared with those who had been operated by general surgeons or gynecologists (36 months v 30 months, $P < .003$; Fig 3). In our patient cohort, initial effort at surgical resection was performed by a nongynecologic oncological specialist in 28% of the patients (Table 2). We have a team of oncosurgeons who are trained in doing extensive cytoreductive surgeries, including complex multiorgan extirpations. The impact of their surgical effort was clearly reflected in the survival outcomes in these patients. Interval cytoreduction after a course of neoadjuvant chemotherapy has been shown to be noninferior to primary cytoreduction in a number of phase III trials,^{26,27} although a number of other studies have favored the use of primary cytoreduction wherever feasible.^{28,29} Because of this reason, there is a general bias among surgeons favoring upfront surgery. Consequent to this, few more studies have been initiated to solve this enigma.^{30,31} Analysis of our data revealed favorable impact of upfront surgery on survival, which can be attributed partially to selection bias.

Decreasing survival was observed with advancing stage. Median OS was 72 months for stage I and decreased to 20 months in stage IV disease. Median PFS was 18 months for the entire study cohort. Treatment outcomes of patients with epithelial OC observed in this study are inferior compared with Western patient cohorts.^{10,32} In the Indian subcontinent, median OS is still lower than Western patient cohorts. This may be due to lack of all available treatment options, less access to tertiary care facilities, trained

surgical oncologist, and stage of disease at presentation. The availability of newer systemics and molecular pathological testing (such as BRCA, etc) is still limited to few pockets in big cities, with prohibitively high costs.³³ The incorporation of antiangiogenic drugs (bevacizumab) and PARP inhibitors have shown survival benefit in many studies in advanced ovarian cancer.⁷ However, drugs like bevacizumab were scarcely used in these patients, and none of them received PARP inhibitors at any point of time, because of resource constraints. The situation is further compounded by the absence of resource specific national guidelines for the treatment of OC. The oncologists in India use guidelines like those of National Comprehensive Cancer Network, European Society for Medical Oncology etc, which have been developed for treatment of patients with possibly a different pharmacogenetic makeup from that of Indian population in a different socioeconomic milieu. Nonetheless, these developments are being

gradually absorbed in the routine clinical practice in India. Lately, National Cancer Grid in India has proposed guidelines adopted for Indian patients, keeping their financial and socioeconomic milieu into consideration.

Our report, being a retrospective study conducted in a tertiary-level institute of the region, is fraught to be affected by referral and selection biases. However, its main strengths are the number of patients and a relatively decent follow-up period. Furthermore, almost all of these patients have been assessed in multidisciplinary board meetings at some point in their clinical course, ensuring relatively uniform management approach.

In conclusion, the patterns of presentation and outcomes in our patient cohort were similar to what is noted in most of the studies from the rest of the country and reflect the late presentation and overall poor outcomes associated with this disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://OpenPayments)).

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