

Outcomes and Long-term Follow-up of Epithelial Ovarian Cancer: Experience from the Lead Cancer Center of Pakistan

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Introduction

In Pakistan, ovarian cancer ranks as the second most common cancer that affects women (1). It is collectively referred to as an epithelial cancer that arises from the ovary, fallopian tube, or peritoneum. The majority of ovarian cancers (95%) are epithelial adenocarcinomas, which are histologically subclassified as high-grade serous, low-grade serous, clear cell, mucinous, and endometrioid serous, while the remaining cancers arise from other ovarian cell types, including sex cord-stromal tumors and germ cell tumors.

Ovarian cancers are surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria (3). These cancers differ significantly in their prognosis and risk factors. In early stages, the primary treatment is surgery to remove the ovaries, including fallopian tubes, and uterus, as well as to assess for any metastasis. However, in advanced stages, the goal of surgery is “debulking,” which is intended to remove as much of the tumor as possible, including the ovaries, fallopian tubes, uterus, and possibly affected organs like bowel, lymph nodes, and omentum. Adjuvant chemotherapy aims to eliminate the microscopic metastatic disease remaining after surgery. Moreover, there is a role for neoadjuvant chemotherapy and interval surgery when optimal debulking is unlikely, the patient is not fit for surgery, or the patient refuses upfront surgery. The survival outcomes decrease dramatically when the disease spreads beyond the pelvic cavity and progresses into advanced stages (FIGO stages III and IV). The reported 5-year survival rate is around 85%-90% for early stage (FIGO stage I-II) and nearly 10%-30 % for advanced stages of epithelial ovarian cancers⁴. Unfortunately, in our part of the world, more than 70% of patients are diagnosed with advanced stage (5). In low-income countries, treatment of ovarian cancer is more challenging because of patients’

meager access to cancer hospitals, lack of insurance, refusal of treatment, and inability to afford expensive anti-cancer treatment. (6).

This study evaluates the long-term follow-up outcomes of ovarian cancer patients who presented to a high-volume cancer center over a 10-year period. To our knowledge, this is the first report of long-term follow-up data on epithelial ovarian cancer in this context.

Material and Methods

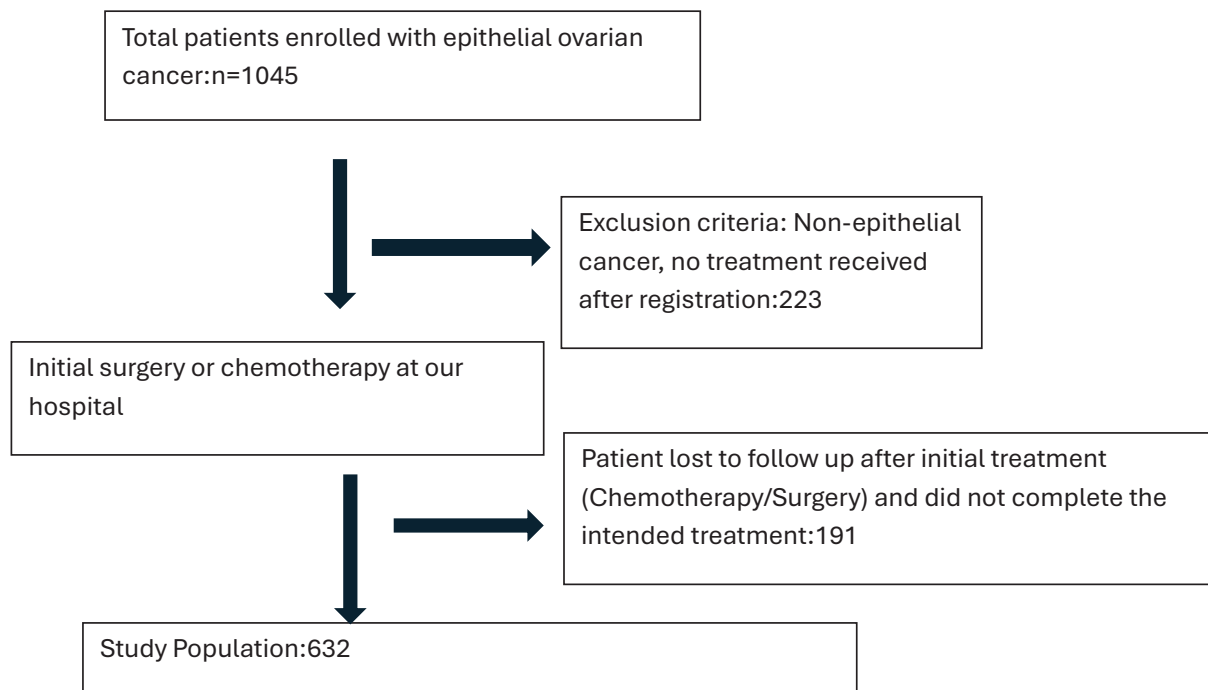
A retrospective chart review of patients with ovarian cancer was performed using our institution’s prospectively maintained database after obtaining approval from our Institutional Review Board. This study included all patients with newly diagnosed FIGO stage I-IV ovarian, fallopian tube, or primary peritoneal cancer who underwent initial treatment at SKMH between 1 January 2011 and 31 December 2020.

All patients with a non-epithelial ovarian tumor, carcinosarcoma, and those who did not complete their proposed treatment after diagnosis were excluded (See flow chart, selection of patients’ population Figure 1). Patients with borderline ovarian tumors were excluded from the analysis.

Data on patient demographics, clinicopathological characteristics, treatment modalities (including surgery or anti-neoplastic therapy), and survival outcomes were systematically compiled. All patients eligible for chemotherapy received platinum-based chemotherapy, carboplatin (AUC 5-6) and paclitaxel (175 mg/m²) every 3 weeks for 6 cycles.

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Figure 1. Selection of study population. A total of 1045 patients with epithelial ovarian cancer were enrolled from January 2011 to December 2020. After exclusions, 631 patients comprised the final study population.



Optimal cytoreduction, as defined by the Gynecologic Oncology Group, is residual disease with a maximum tumor diameter < 1 cm. Suboptimal cytoreduction was defined as any residual tumor nodule measuring > 1 cm in maximal diameter. This classification follows the standard criteria established by the Gynecologic Oncology Group (GOG) (7).

Patients with a platinum-free interval (PFI) of six months or longer are considered to have “platinum-sensitive” disease, while those with a PFI of less than six months are considered to have “platinum-resistant” disease (8). Progression-free survival (PFS) and overall survival (OS) were calculated. PFS was defined as the duration from primary surgery or first cycle of chemotherapy (whichever occurred first) to the earliest of disease recurrence or progression, last follow-up, or death (whichever occurred first).

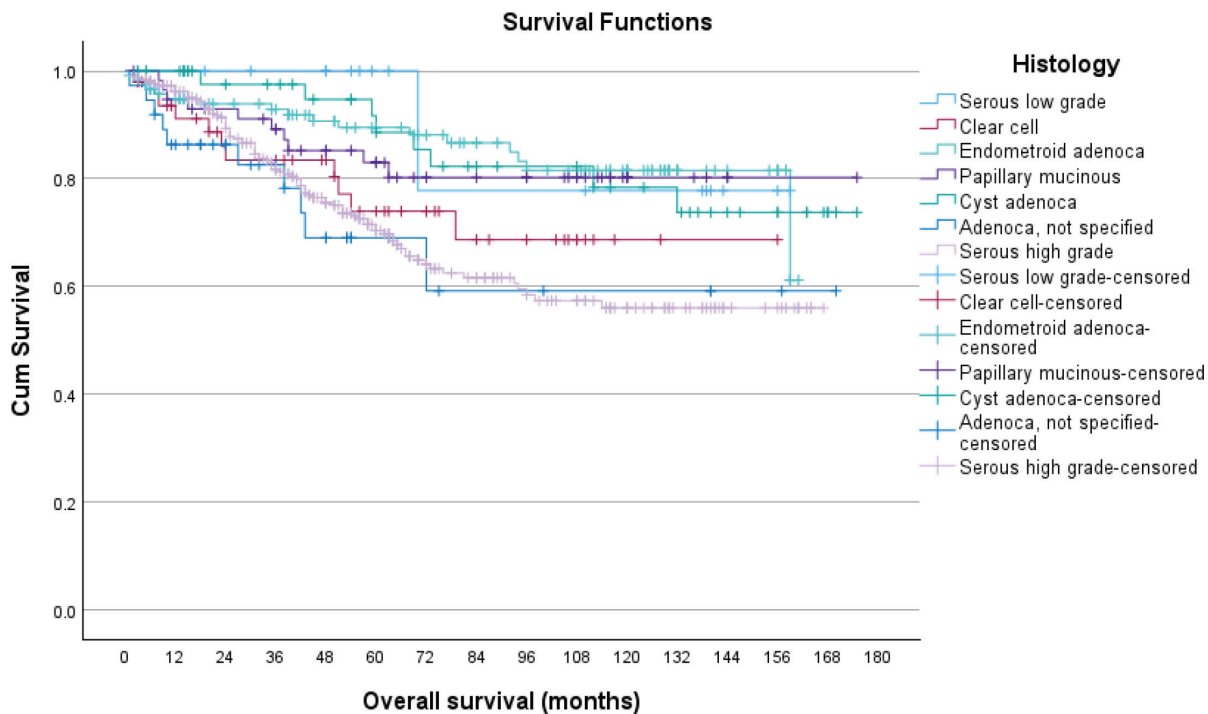
Overall survival (OS) was defined as the interval from the date of primary surgery or first cycle of chemotherapy (whichever was received first) to the last follow-up, or death (whichever occurred first). For PFS, the outcomes of interest were patients who died and those alive with disease progression; for OS, the outcome of interest was death. We included only those patients whose deaths were confirmed to be attributable to ovarian cancer. Comparisons of the survival distributions were made according to the CA-125 levels (≤ 100 and > 100 U/ml), histological subtypes

of ovarian cancer, and disease stage. The Kaplan-Meier method was used to estimate median survival time across all FIGO stages, as well as histopathological types and P values in survival analyses were calculated using the log-rank test based on the Cox proportional hazard model. The results were considered significant at the 0.05 alpha level. The Statistical Package for Social Sciences version 26 was used to conduct the analysis (Figure 2). Institutional Review Board (IRB) approval for this study was obtained from SKMCH & RC, Pakistan, with the exemption number (EX-13-01-26-01).

Results

Patient Populations

A total of 632 patients were included in the analysis after excluding the ineligible patients (Figure 1). The median age of the study population was 51 (18–87) years. Abdominal pain was the most common symptom at presentation in 534 (84.6%), while the most prevalent histological type was high-grade serous (46.8%). Stage IIIA (146, 23.1%) and IA (129, 20.4%) were the most common stages at presentation. The baseline CA-125 was less than 100 U/ml in about half of the patients. (Table 1).

Figure 2. Overall survival according to histological subtype in patients with epithelial ovarian cancer.

The Kaplan-Meier analysis

For the PFS, the Kaplan-Meier curves, testing for the equality of progression-free distributions for different levels of categorical variables, based on Log Rank (Mantel-Cox), showed that there was a significant difference according to age group ($p=.03$), CA-125 category ($p<.001$), histology type ($p<.001$), stage at presentation: I vs. II ($p=.003$), I vs. III ($p<.001$), and II vs. III ($p<.001$)) (Figure 3).

For overall survival distributions, the Kaplan-Meier analysis showed the following results: there was no significant difference according to age group ($p=.33$) and relapse type ($p=.57$), but the differences were statistically significant according to CA-125 category ($p<.001$), histology ($p<.001$), stage at presentation between I and II ($p<.001$), I and III ($p<.001$), I and IV ($p<.001$), II and III ($p=.007$), II and IV ($p=.02$), and III and IV ($p=.01$).

Cox regression analysis

For PFS, the overall Cox proportional hazards model was statistically significant ($\chi^2(8) = 22.31$, $p = .004$), indicating that the included predictors, as a group, significantly improved the model's predictive ability relative to the null model with no predictors. The outcomes of interest were recurrence and death. In the multivariable Cox model (enter method), only the CA-125 category was significantly associated with progression-free survival (HR=1.48, 95%

CI 1.07–2.04, $p=.02$). Age group (HR=.77, 95% CI .58–1.01, $p=.06$); presenting stage ($p=.09$) with stage III vs. I (HR=1.43, 95% CI .99–2.06, $p=.06$); and relapse type (HR=1.38, 95% CI=.96–1.99, $p=.08$) showed borderline associations but were not statistically significant predictors (all with a $p > 0.05$). Nor were other variables. The details are shown in Table 2.

For OS, the overall Cox proportional hazards model was not statistically significant ($\chi^2(10)=18.09$, $p=0.053$), indicating that the included covariates, as a group, did not significantly improve model fit relative to the null model. The outcome of interest was death. The multivariable Cox regression analysis (enter method) was performed for the seven predictors and the interaction term under consideration. The subcategories of the covariate 'stage,' stage IV vs. stage I (HR=2.24, 95% CI 1.11–4.54, $p=.02$) and stage III vs. stage I (HR=1.79, 95% CI 1.01–3.17, $p=.04$), and time-dependent covariate (platinum resistant vs. sensitive (HR=.97, 95% CI=.94–.99, $p=.03$)) were significantly associated with the survival time (hazard of death). The details are shown in Table 3.

Discussion

The burden of ovarian cancer is higher in developing countries like Pakistan, as it is the second most common cancer in

Table 1. Patients baseline characteristics.

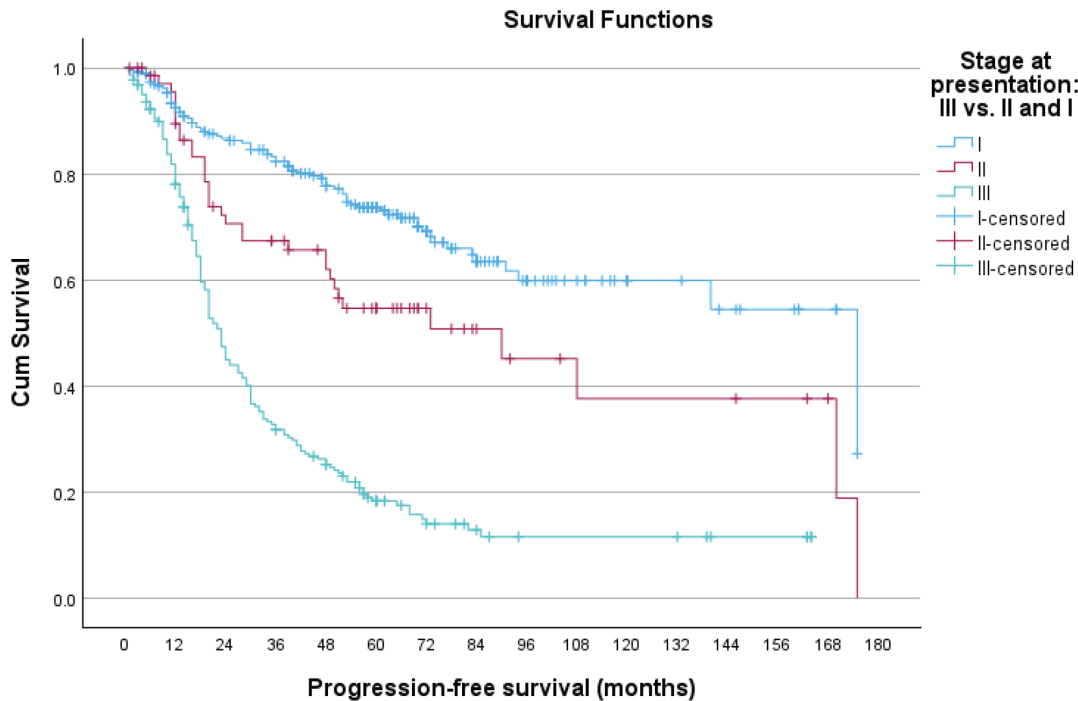
Age Mean	51 years (18-87)	
Stage		
IA	129	20.4%
IB	26	4.1%
IC	108	17.1%
IIA	38	6.0%
IIB	16	2.5%
IIC	17	2.7%
IIIA	60	9.5%
IIIB	13	2.1%
IIIC	146	23.1%
IV	78	12.4%
Symptoms at diagnosis		
Abdominal Pain	534 (84.6%)	
PV Bleed	259 (51.0%)	
Bloating	164 (26.0%)	
Incidental	21 (3.3%)	
Histological Cell Type		
Serous (High grade)	297 (46.8%)	
Serous (Low grade)	19 (3.0%)	
Mucinous	58 (9.2%)	
Clear Cell	50 (7.9%)	
Endometrioid	121 (19.2%)	
Cyst Adenocarcinoma	50 (7.9%)	
Unclassified	38 (6.%)	
CA-125 at Presentation		
<= 100	331 (52.5) %	
> 100	291 (46.1%)	
N/A	9 (1.4%)	
Initial Surgery		
Optimal Surgery	297 (47.1%)	
Suboptimal Surgery	295 (46.6%)	
N/A	40 (6.3%)	
Chemotherapy		
Neoadjuvant Chemotherapy	213 (33.75%)	
Adjuvant Chemotherapy	263 (41.67%)	
N/A	155 (24.56%)	
Maintenance Therapy		
Bevacizumab	68 (10.77%)	
Olaparib (PARPi)	13 (2.06%)	
Recurrence or Death		
Yes	341 (54%)	
No	283 (44.8%)	
Died du to other reason	8 (1.3%)	
Type of recurrence		
Platinum Sensitive	255 (40.4%)	
Platinum resistant	60 (9.7%)	
N/A	315 (49.9%)	
Current status		
In remission	197 (31.2%)	
Alive with disease progression	83 (13.13%)	
Lost to follow up	205 (32.4%)	
Dead	147 (23.25%)	

women 1. The battle against this challenge is complicated by the aggressive nature of the disease, delayed diagnosis, and impaired nutritional state of the patient. Moreover, survival is further affected by a lack of resources, therapeutic competence, and treatment decline. In early-stage ovarian cancer, patients usually present with nonspecific symptoms such as irregular

menstruation, in premenopausal women, bloating, and urinary symptoms (9).

In advanced stages, patients present with symptoms that include abdominal pain, emesis, bloating, early satiety, anorexia, constipation, and dyspnea (10). In developed countries, the mean age at diagnosis is 63 years. In the current study, the mean age at diagnosis is 51 years, which is in concordance with the early onset of cancer in our part of the world (11,12). Serous histology is the most common type of ovarian cancer in the current series, as seen in previous ovarian studies (13,14). As in most series, most of our patients had stage III or IV at presentation¹⁵. Abdominal pain was the most common symptom at presentation, followed by per vaginal bleeding as seen in previous studies (16).

Cancer Antigen 125 (CA-125) is the most widely used tumor marker for EOC and is FDA-approved for monitoring treatment response (17). In the current study, we evaluated the role of high and low CA-125 levels on the prognosis of ovarian cancer and noted that the patients with high CA-125 levels had a poorer prognosis as compared to those with low CA-125 at the time of diagnosis. Our study showed that patients with high CA-125 at presentation had lower survival than those with low CA-125. However, some studies have shown that CA 125 has a low overall sensitivity and specificity in the diagnostic of EOC (19). EOC substantially impacts survival, with high-grade serous being the most common, aggressive, and lethal cancer as compared to the other histological subtypes of EOC¹²⁰, (21). The current study also confirmed the above findings, with high-grade serous tumors being the more aggressive and the most common type of epithelial ovarian cancer. Overall survival was significantly different in high-grade serous cancers as compared to the other histologies (Figures 4 and 5) ($P < 0.001$). In EOC, the presentation stage is the main determinant of survival (22). The early-stage/early-stage O I/II has significantly improved outcomes (e.g., 5-year survival around 90%) compared with around 35% for those with advanced-stage EOC (FIGO III/IV) (23,24). In the current study, the 5-year survival for stage I/II EOC is similar to the above findings (Figures 5 and 6). However, in advanced stages, the outcomes in the current study are better than those reported in previously published studies. This is likely due to the younger population in this study, as previous studies have shown better outcomes, even in advanced-stage EOC, in younger patients (25). Therefore, large multicenter trials for the Pakistani population should be conducted, as the available data are limited. In the current study, the majority of patients had advanced disease at presentation, which is consistent with previous studies from South Asian countries. 26,2 However, the current study is constrained by the inherent limitations of its retrospective design and single-institution study, as well as missing information on the type of treatment received. Moreover, the major concern was the availability of

Figure 3. Progression-free survival according to stage at presentation.**Table 2.** Multivariate analysis for progression free survival.

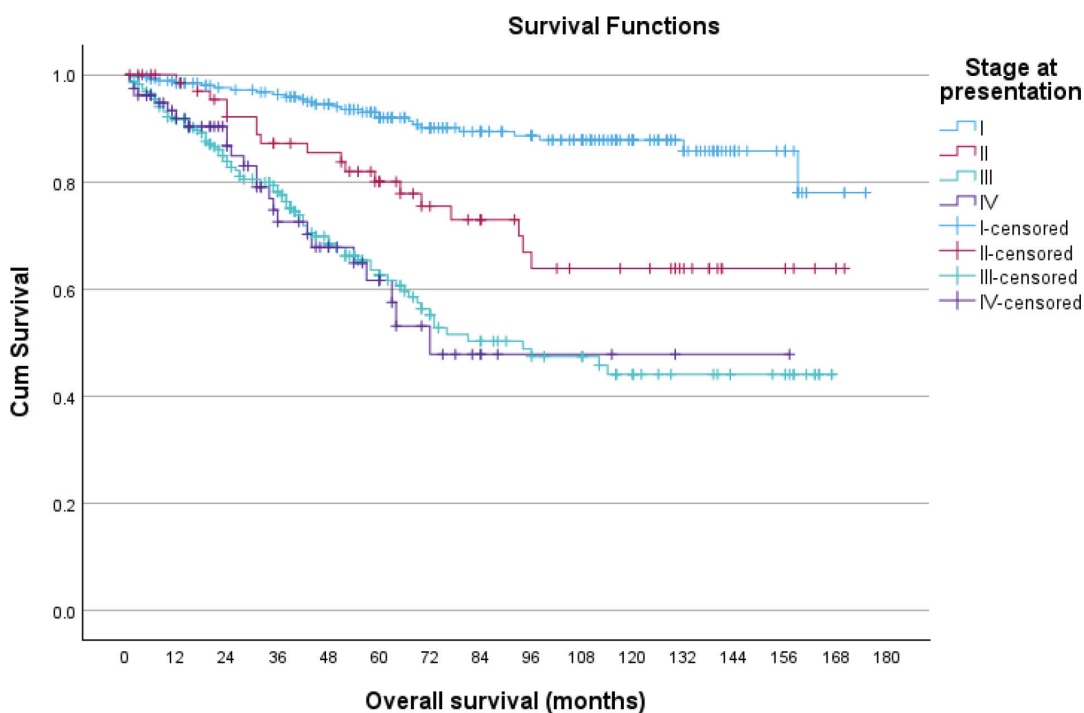
Progression-free survival	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age: > 50 vs. ≤ 50 years (referent)	-.262	.141	3.461	1	.063	.769	.583	1.014
CA 125: > 100 vs. ≤ 100 units/mL (referent)	.389	.165	5.546	1	.019	1.476	1.067	2.040
Histology: serous high-grade ca vs. all other types (referent)	-.062	.145	.186	1	.666	.939	.707	1.248
Stage at presentation: III vs. II and I (I was the referent)			4.661	2	.097			
Stage at presentation: III vs. I	.012	.235	.002	1	.960	1.012	.638	1.603
Stage at presentation: III vs. II	.356	.187	3.625	1	.057	1.428	.990	2.061
Surgery type: Suboptimal vs. optimal (referent)	-.003	.158	.000	1	.983	.997	.731	1.359
Relapse type: Platinum resistant vs. sensitive (referent)	.323	.186	3.016	1	.082	1.381	.959	1.987

limited information on patients' comorbidities, family history of cancer, and assessment of associated BRCA as well as other genetic mutations. The high rate of loss to follow-up may have

overestimated survival, as patients with poor outcomes were likely unreachable. Due to financial constraints in our Pakistani charity hospital setting, most patients could not afford genetic

Table 3. Multivariate analysis for overall survival.

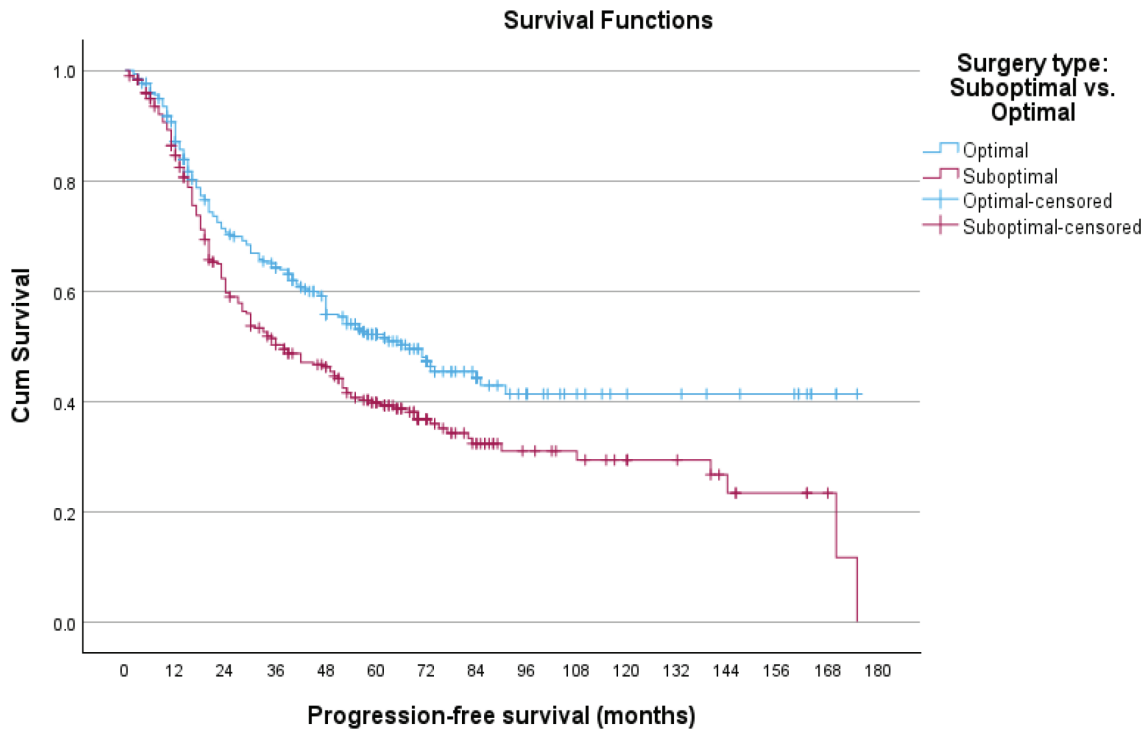
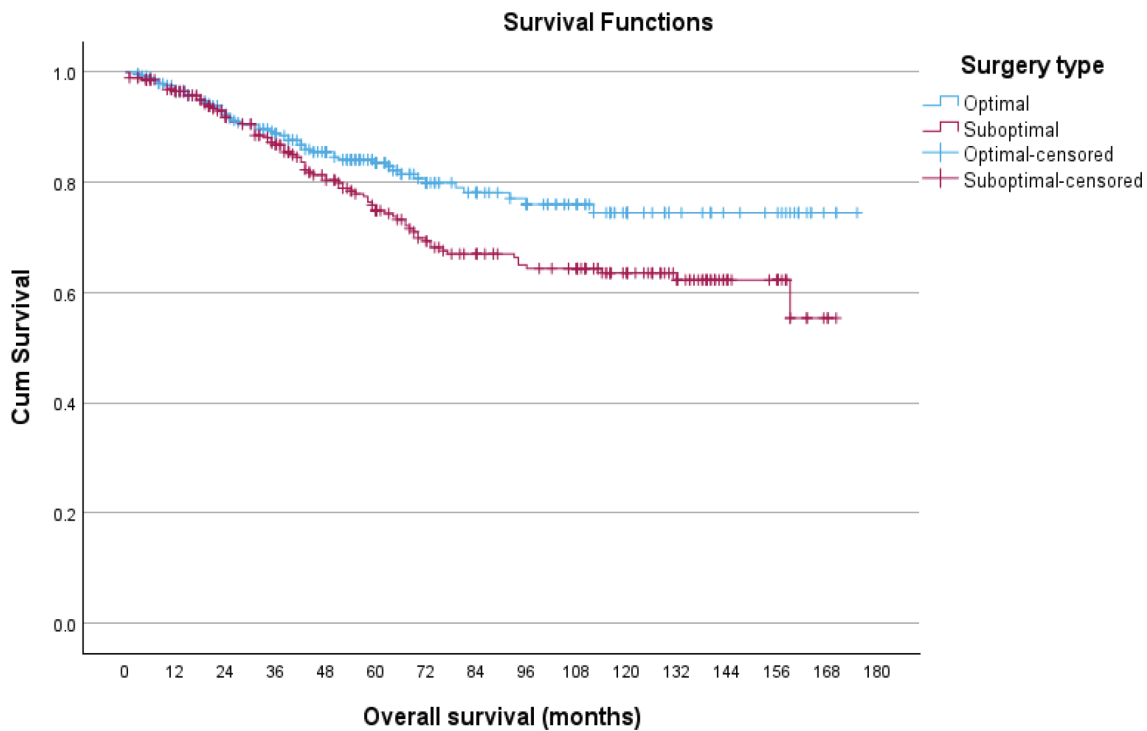
Overall survival	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age: > 50 vs. ≤ 50 years (referent)	-.231	.194	1.414	1	.234	.794	.542	1.162
CA 125: > 100 vs. ≤ 100 units/mL (referent)	.092	.225	.167	1	.683	1.096	.706	1.703
Histology: Serous high-grade ca vs. all other types (referent)	-.047	.202	.055	1	.815	.954	.642	1.417
Stage at presentation: IV, III, and II vs. I (I was the referent)			5.698	3	.127			
Stage at presentation: II vs. I	.579	.344	2.839	1	.092	1.784	.910	3.498
Stage at presentation: III vs. I	.583	.291	4.027	1	.045	1.792	1.014	3.168
Stage at presentation: IV vs. I	.808	.359	5.064	1	.024	2.244	1.110	4.536
Type of surgery: suboptimal vs. optimal (referent)	.144	.213	.458	1	.498	1.155	.761	1.754
Relapse: platinum resistant vs. sensitive (referent)	1.062	.548	3.758	1	.053	2.891	.988	8.455
T_COV_ (relapse*time)	-.034	.016	4.577	1	.032	.967	.937	.997

Figure 4. Overall survival according to stage at presentation.

testing or advanced therapies such as bevacizumab and PARP inhibitors.

In conclusion, ovarian cancer has been described as the leading cause of mortality from gynecologic cancers, and there is insufficient evidence about the epidemiology of EOC cancer

in Pakistan. We have shown that, in our part of the world, patients are younger and have an advanced stage at the time of diagnosis. We also found that in EOC, the long-term survival is associated with low CA-125, non-serous epithelial ovarian cancer, and early stage at diagnosis.

Figure 5. Progression-free survival in patients undergoing suboptimal versus optimal primary debulking surgery.**Figure 6.** Overall survival in patients undergoing suboptimal versus optimal primary debulking surgery.

Funding

The project was not funded by any external party.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgements

We are grateful to Dr. Irfan Kabir, consultant surgical oncologist at SKMH&RC, for his wonderful support and input in the preparation of this manuscript.

Author Contributions

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Conception or design of the work: JA, MR, JK, MUKA

Acquisition, analysis, or interpretation of data for the work: FB, JA,

Drafting the work or revising it critically for important intellectual content: JA, MUKA, MR

Final approval of the version to be published: JA, MUKA

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