Outcome and prognostic factors of low-grade serous ovarian cancer: An observational retrospective study

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Abstract. Low-grade serous ovarian cancer (LGSOC) is a very rare histological subtype of serous ovarian cancer, representing ~2% of all epithelial ovarian cancer cases. LGSOC has a better prognosis but a lower response rate to chemotherapy in comparison to high-grade serous ovarian carcinoma (HGSOC). The present study is a retrospective review of the medical records of all patients with histologically proven LGSOC diagnosed and treated in a single institute between January 2003 and December 2019. A total of 23 patients diagnosed with LGSOC and treated at King Faisal Specialist Hospital and Research Center (Riyadh, Saudi Arabia) were identified. The median age at diagnosis was 45.5 years (range, 26-66 years) and the median body mass index was 26.1 (range, 18-43). A total of 21 patients (91.3%) had *de novo* LGSOC, whereas only 2 patients (8.7%) had LGSOC that had transformed from serous borderline ovarian tumors and recurred. A total of 8 patients (34.8%) were diagnosed with International Federation of Gynecology and Obstetrics stage IV, whereas 3 (13.0%), 3 (13.0%) and 9 (39.1%) were diagnosed with stages I, II and III, respectively. In addition, 10 (43.5%), 5 (21.7%), and 3 (13.0%) patients had complete response, stable disease and partial response statuses after first-line therapy, respectively. At a median follow-up time of 34 months [95% confidence interval (CI), 25.32-42.69], the median progression-free survival (PFS) time was 75.2 months (95% CI, 17.35-133.05) and the median overall survival (OS) time was not reached. In conclusion, LGSOC exhibited better PFS and OS times than HGSOC as compared with data from the literature, and there is the option for systemic treatment (chemotherapy or hormonal therapy). Optimal cytoreduction showed numerically higher, but non-significant, PFS and OS times compared with suboptimal debulking; however, the optimal systemic chemotherapy or hormonal treatment remains controversial.

Introduction

Low-grade serous ovarian cancer (LGSOC) is an understudied rare disease that is a distinct pathological and clinical entity representing 2% of all epithelial ovarian cancer cases and 4.7% of serous ovarian cancer cases globally (1). LGSOC is associated with reduced aggressive biological behavior, a lower sensitivity to chemotherapy and a more prolonged overall survival (OS) time compared with high-grade serous ovarian carcinoma (HGSOC) (2). Due to changes in the diagnostic criteria and the consequent diagnostic shift from LGSOC to serous borderline ovarian tumors (SBOTs), the proportion of LGSOC diagnoses has decreased by 3-4% per year while the proportion of SBOTs has increased (3).

Microscopically, LGSOC is characterized by a consistent population of cuboidal, low columnar and occasionally flattened cells with an amphophilic or lightly eosinophilic cytoplasm. In addition, LGSOC is associated with mild to moderate atypia, with ≤12 mitoses per 10 high-power fields. Destructive invasion by neoplastic cells can be detected in a ≥3.0 mm area (linear dimension) of the tumor/ovarian stroma or in an area with desmoplasia. Furthermore, psammoma bodies occur often in LGSOC and with high frequency (4).

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The presence of invasive implants in patients with ovarian serous borderline neoplasms is now classified as LGSOC due to similar overall survival times (5).

Age at diagnosis, body mass index (BMI), smoking status and stage at diagnosis are all considered important prognostic factors in women diagnosed with LGSOC (6-8).

According to Shvartsman *et al* (9), women with *de novo* LGSOC have a similar survival time to those who had a prior SBOT that underwent a malignant transformation to LGSOC.

Optimal cytoreductive surgery is the cornerstone in the primary management of all stages of LGSOC. If unresectable disease is found or if the patient is not fit for surgery (due to comorbidities, age or nutritional status), then treatment with neoadjuvant chemotherapy and subsequent interval debulking surgery may be considered once the disease has been histologically confirmed (10). Adjuvant therapies are not indicated for stage IA-IB after comprehensive surgical staging (11). Notably, LGSOC has an indolent behavior and appears to be less responsive to chemotherapy, both as a first-line treatment and when used to treat recurrence, compared with HGSOC (1,8,12-15). However, women with LGSOC may benefit from hormonal treatment (16-19).

Although it is relatively chemoresistant, adjuvant platinum-based chemotherapy is still the standard of care for LGSOC, while hormonal maintenance therapy following adjuvant chemotherapy can confer an improved outcome. Disease recurrence may be treated using secondary cytoreductive surgery, hormonal therapy, chemotherapy, targeted therapy and therapies in clinical trials. Notably, genomic studies and targeted therapies are expected to bring about enhancements for the overall treatment of LGSOC (4).

The present retrospective study aims to present the experience of a single institute with regard to the management and survival of a cohort of women diagnosed with LGSOC.

Patients and methods

Study design. The present study is a retrospective study with the aim of reporting real-world, single-institution experiences of LGSOC management, to evaluate the clinicopathological characteristics, treatment and long-term survival of LGSOC, and to determine prognostic factors affecting survival.

The primary objectives were to evaluate the efficacy of treatment modalities used in cases of LGSOC in terms of progression-free survival (PFS) and OS. The secondary objectives were to assess baseline characteristics and prognostic factors affecting survival.

Procedure and data collection. The medical records of patients with histologically proven LGSOC diagnosed and treated at King Faisal Specialist Hospital and Research Center (KFSHRC) (Riyadh, Saudi Arabia) between January 2003 and December 2019 were reviewed. All patients were diagnosed histologically at the institution, and those cases that were initially diagnosed outside, but treated inside, the institution were pathologically reviewed by pathologists of the institution to confirm the diagnosis. Retrospectively, the electronic charts of the patients were examined, and the following information was entered in RedCap (https://redcap.kfshrc.edu.sa): Patient demographics, presenting symptoms and signs, International Federation of Gynecology and Obstetrics (FIGO) stage (20), histology, subsequent management and outcome.

Patient characteristics were collected, such as age, clinical presentation, parity, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (21), BMI as per World Health scale (underweight, <18.5 kg/m^2; normal weight, 18.5-24.9 kg/m^2; overweight, 25-29.9 kg/m^2; obese, 30.0-30.9 kg/m^2; and extremely obese, ≥40 kg/m^2) (22), Tumor-Node-Metastasis staging (23), FIGO staging at initial presentation, surgery, surgical outcome, adjuvant therapy, response rate, disease progression, and survival outcome. Radiographic responses were assessed retrospectively by a radiologist according to Response Evaluation Criteria in Solid Tumors v1.1 (24). The response in patients with non-measurable disease was categorized according to the decision made by the treating physician.

Statistical analysis. Patient characteristics are presented using frequencies with percentages for categorical variables and medians with interquartile ranges for continuous variables. Fisher's exact test was performed to test the distribution of different risk factors among treatment groups. Probabilities of OS were summarized using the Kaplan-Meier estimator with variance calculated using the Greenwood formula. Survival curves were compared using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference. All statistics were performed using SPSS® Version 20 for Windows (IBM Corp.).

PFS time was calculated from the start of treatment until the date of radiological progression, death, or last follow-up. OS time was calculated from the start of treatment to death or last follow-up. Patients lost to follow-up were censored at the date of their last follow-up. PFS and OS were analyzed according to age, BMI (<25 or ≥25), primary site (unilateral ovarian, bilateral ovarian or primary peritoneal cancer), cancer antigen 125 (CA125) level (normal ≤35 U/ml or high >35 U/ml), optimal surgery (<1 cm residual) vs. suboptimal surgery (>1 cm residual), and presence of lymphovascular invasion (LVI) or perineural invasion (PNI).

Ethical considerations. This project was conducted according to the principles of the Declaration of Helsinki (2000), Good Clinical Practice Guidelines, and the policies and guidelines of the Research Advisory Council at KFSHRC, and was approved by the Medical Ethics Committee (approval no. 2231168). The identities of the patients remained anonymous, since no identifying data or protected health information was recorded. All data were password-secured to safeguard the confidentiality of the collected patient data. This research was approved for publication by the Office of Research Affairs, and as per the internal regulations of KFSHRC, all authors read and approved the final manuscript.

Results

A total of 23 female patients diagnosed with LGSOC and treated at KFSHRC were identified. The patient characteristics are shown in Table I. The median age at diagnosis was 45.5 years (range, 26-66 years) and the median BMI was 26.1 kg/m^2 (range, 18-43 kg/m^2). Notably, most patients (78.3%) had an ECOG PS of 0-1 at diagnosis. Most of the patients

Table I. Patient characteristics (n=23).

Characteristic	Value
Age, years	
Median	45.5
Range	26-66
BMI, kg/m^2	
Median	26.1
Range	18-43
ECOG PS, n (%)	
0	8 (34.8)
1	10 (43.5)
2	3 (13.0)
Unknown	2 (8.7)
Presenting symptoms, n (%)	
Abdominal pain	17 (73.9)
Constitutional symptoms	5 (21.7)
Pelvic symptoms	2 (8.7)
Urinary symptoms	2 (8.7)
Dysmenorrhea	1 (4.3)
Infertility	2 (8.6)
Gastric outlet obstruction	1 (4.3)
Pulmonary Embolism	1 (4.3)
Incidental finding (asymptomatic)	9 (39.1)
Parity, n (%)	
Nulliparous	6 (26.1)
Multiparous	13 (56.5)
Unknown	4 (17.4)
Comorbidities, n (%)	
PCOS	1 (4.3)
Hypertension	4 (17.4)
DM	7 (30.4)
Primary infertility	5 (21.7)
Ascites, n (%)	
No	8 (34.8)
Yes	11 (47.8)
Unknown	4 (17.4)
Primary site, n (%)	
Unilateral ovarian	9 (39.1)
Bilateral ovarian	7 (30.4)
Primary peritoneal	7 (30.4)
Baseline CA125, U/ml	
Median	275.5
Range	10.3-9482
Anemia, n (%)	
Yes	7 (30.4)
No	16 (69.6)
Surgical outcome, n (%)	
Optimal debulking <1 cm residual	13 (56.5)
Non-optimal debulking >1 cm residual	10 (43.5)
FIGO stage at presentation, n (%)	
I	3 (13.0)
II	3 (13.0)
III	9 (39.1)
IV	8 (34.8)
T stage, n (%)	
T1	2 (8.7)
T2	2 (8.7)
T3	7 (30.4)
Tx	12 (52.2)
N stage, n (%)	
N0	4 (17.4)
N1	1 (4.3)
Nx	18 (78.3)
M (stage), n (%)	
M0	10 (43.5)
M1	8 (34.8)
Mx	5 (21.7)
Low-grade serous type, n (%)	
De novo low grade	21 (91.3)
Transformed from borderline	2 (8.7)
LVI, n (%)	
No	3 (13.0)
Yes	3 (13.0)
Unknown	9 (39.1)
Missing data	8 (34.8)
Response to first line chemotherapy, n (%)	
CR	8 (34.8)
PR	3 (13.0)
SD	5 (21.7)
PD	3 (13.0)
NA	4 (17.4)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PCOS, polycystic ovary syndrome; DM, diabetes mellitus; CA125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; T, tumor; N, node; M, metastasis; LVI, lymphovascular invasion; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; NA, not available.

(73.9%) presented with abdominal pain. In addition, 5 patients (21.7%) presented with constitutional symptoms, 2 patients (8.7%) with urinary symptoms, 1 patient (4.3%) with dysmenorrhea, 2 patients (8.7%) with infertility, 2 patients (8.7%) with pelvic symptoms, 1 patient (4.3%) with gastric outlet obstruction and 1 patient (4.3%) with pulmonary embolism. A total of 9 patients (39.1%) were asymptomatic and were diagnosed incidentally, and those patients underwent optimal debulking surgery. A total of 21 patients (91.3%) had *de novo* LGSOC, whereas only 2 patients (8.7%) had LGSOC that had transformed from SBOT and recurred. A total of 8 patients (34.8%) were diagnosed with FIGO stage IV, and 3 (13.0%), 3 (13.0%) and 9 (39.1%) were diagnosed with stages I, II and III, respectively. Fisher's exact test was performed to test the distribution of different risk factors among treatment groups. However, no significant differences were shown (Table II).

At a median follow-up time of 34 months [95% confidence (CI), 25.32-42.69], the median PFS time was

Table II. Distribution of risk factors among chemotherapy (n=15) and other treatment (n=8) groups.

Factor	Chemotherapy, n (%)	Others, n (%)	P-value
Age, years			0.612
≤40	8 (53.3)	3 (37.5)	
<40	7 (46.7)	5 (62.5)	
BMI			0.903
<25	6 (40.0)	3 (37.5)	
≥25	9 (60.0)	5 (62.5)	
Stage			0.627
I-II	3 (20.0)	3 (37.5)	
III-IV	12 (80.0)	5 (62.5)	
CA125, U/ml[a]			
≤35	0 (0.0)	1 (14.3)	0.433
>35	8 (100.0)	6 (85.7)	
Primary tumor site[a]			0.990
Bilateral	2 (25.0)	2 (28.6)	
Unilateral	6 (75.0)	5 (71.4)	
Parity[a]			0.992
Nulliparous	3 (37.5)	1 (25.0)	
Multiparous	5 (62.5)	3 (75.0)	

[a]Some data not originally obtained or missing due to the retrospective nature of the study. BMI, body mass index.

75.2 months (95% CI, 17.35-133.05) and the median OS time was not reached (Figs. 1 and 2). Univariate analysis of different subgroups, including age, BMI (<25 or ≥25 kg/m^2), primary site (unilateral ovarian, bilateral ovarian, or primary peritoneal cancer), CA125 (normal ≤35 U/ml or high >35 U/ml), optimal surgery (<1 cm residual) vs. suboptimal surgery (>1 cm residual), and presence of LVI or PNI, showed no statistical significance for PFS and OS. PFS time was significantly higher in patients who received neoadjuvant chemotherapy (P=0.017); however, a significant difference was not achieved for OS (Table III). Multivariate analysis was not performed, as none of the proposed risk factors were significant.

Discussion

LGSOC is a rare histological subtype of ovarian cancer. Notably, women with this type of cancer are often younger and exhibit prolonged survival times compared with those with HGSOC (10). To the best of our knowledge, the present study is the first to present data on LGSOC from the Middle East. The median age of the patients at diagnosis was 45.5 years, which is similar to the retrospective analysis performed by Di Lorenzo *et al* (25). Patients with LGSOC can have different clinical presentations, ranging from an asymptomatic adnexal mass to abdominal pain and distension, with even more symptoms often detected in advanced disease (4). In the present study, 9 patients (39.1%) were asymptomatic; however, 17 (73.9%) had abdominal pain at the initial presentation. In addition, obesity is associated with a higher risk of ovarian cancer (26,27) the median BMI for the patients in the present study was 26.

Different studies have shown that LGSOC is an indolent disease with prolonged survival times compared with HGSOC (4,8,28,29,30). At a median follow-up time of 34 months (95% CI, 25.32-42.69) in the present study, the median PFS time was 75.2 months (95% CI, 17.35-133.05) and the median OS was not reached. In a previous retrospective study comparing the outcomes of women with HGSOC and LGSOC, the median OS time was 40.7 months among patients with high-grade tumors and 90.8 months among women with low-grade tumors (29). The median OS time for stage II-IV LGSOC as previously reported to be 97.8 months based on information from the MD Anderson LGSOC Database (8). The median OS time for women with stage III and IV HGSOC as reported to be 39 months in the Gynecologic Oncology Group (GOG) 218 study (30).

Certain factors influence outcome in patients with LGSOC, including age, FIGO stage and undergoing optimal cytoreductive surgery (31,32). In the present study, 43.5% of women had residual disease after cytoreductive surgery, and ~87.0% of patients presented with advanced stage (II-IV) disease. Patients aged ≤40 years comprised 34.8% of the study population. These three factors did not show a statistically significant effect on PFS and OS in the study, possibly due to it being an analysis of a rare disease in a small number of patients. LGSOC of peritoneal origin occurred in 30.4% of the patients; in general, this is associated with worse outcomes as compared with LGSOC of ovarian origin (33,34).

LGSOC is considered relatively chemoresistant compared with HGSOC (34). In one study, the overall response rate was 4% and stable disease was observed in >60% of treated patients (4). In the adjuvant setting, the overall response rate, including complete and partial response, has been reported to reach 25%

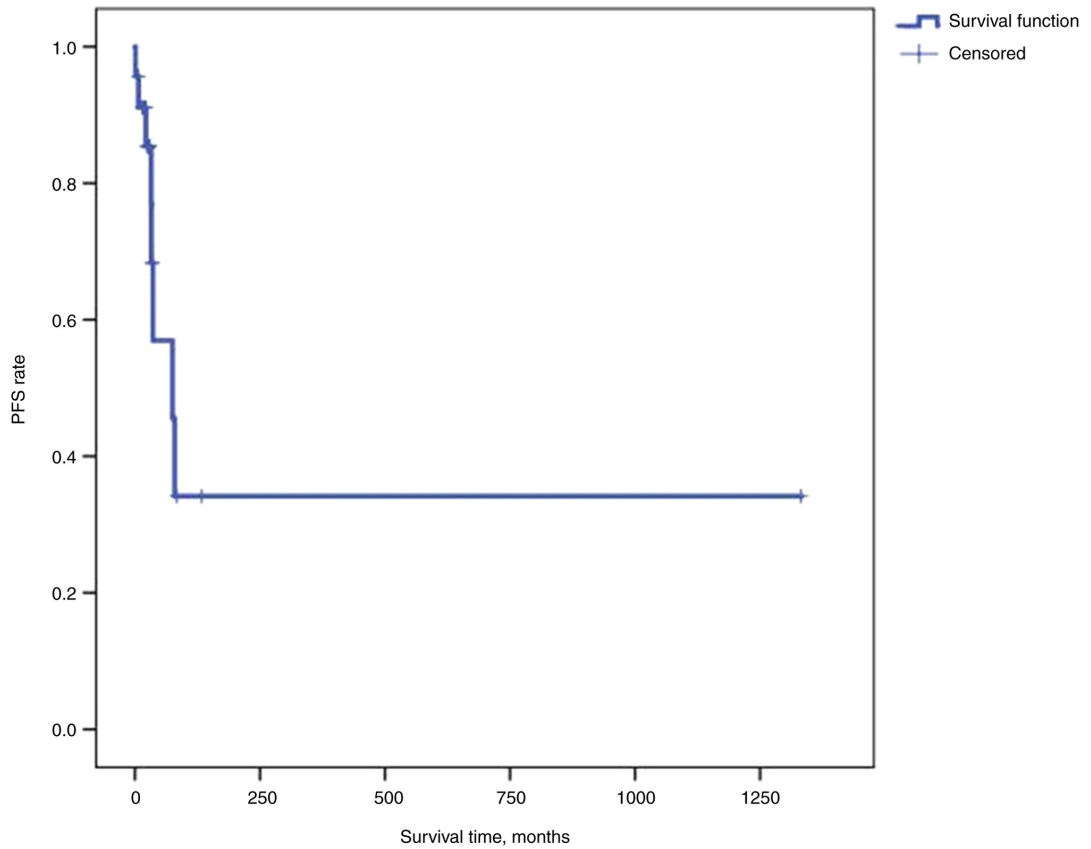

Figure 1. PFS curve. PFS, progression-free survival.

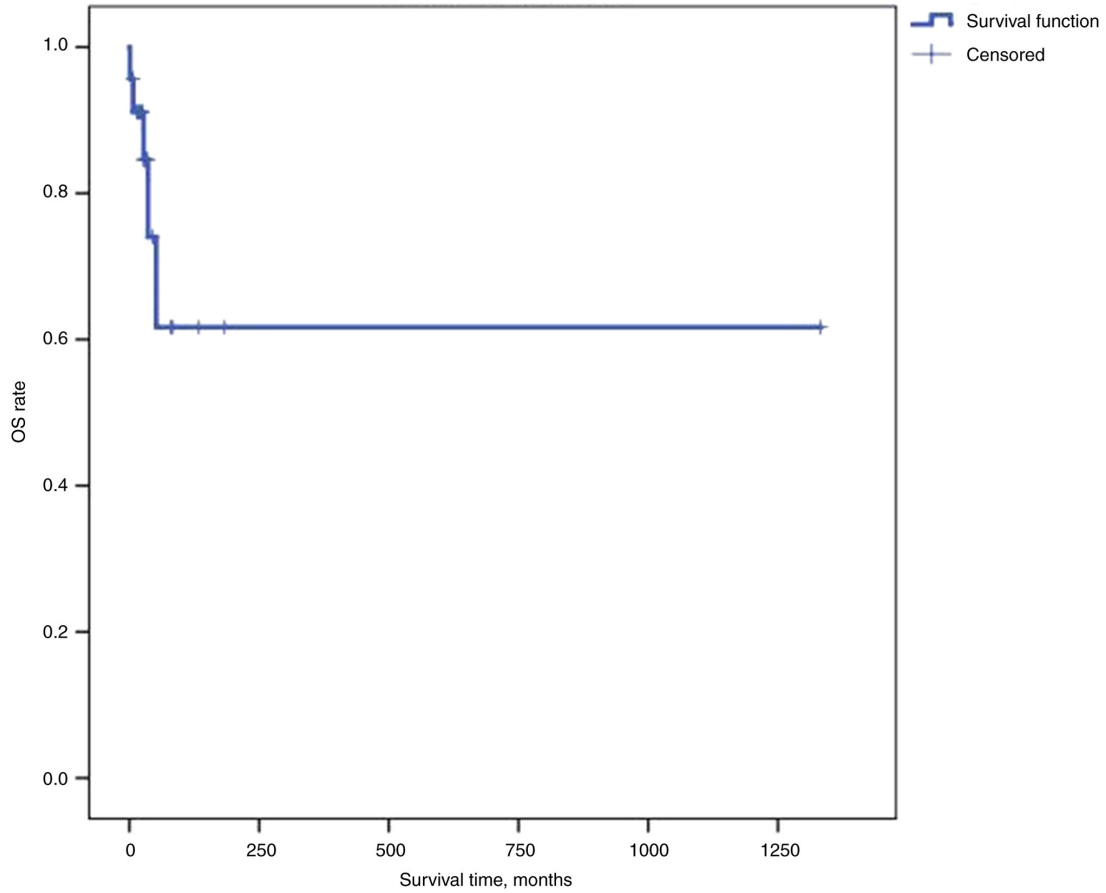

Figure 2. OS curve. OS, overall survival.

Table III. Univariate analysis of different prognostic factors in patients with low-grade serous ovarian cancer.

	PFS		OS	
Factor	Median (95% CI), months	P-value	Median OS (95% CI), months	P-value
Chemotherapy		0.017		0.251
Neoadjuvant	NR (-)		NR (-)	
Adjuvant	32.361 (10.864-53.859)		51.647 (14.517-88.777)	
Surgery		0.801		0.466
Optimal debulking	75.203 (32.228-118.175)		NR (-)	
Non-optimal debulking	36.074 (28.734-43.414)		NR (-)	
BMI		0.804		0.338
<25	36.074 (30.815-41.333)		51.647 (26.467-76.827)	
≥25	4.400 (4.260-4.540)		NR (-)	
CA125, U/ml		0.324		0.232
<35	21.881[a]		27.335[a]	
≥35	75.203 (18.000-132.400)		NR (-)	
Laterality		0.190		0.343
Bilateral	75.203[a]		NR (-)	
Unilateral	32.821 (0.000-75.824)		NR (-)	
Parity		0.682		0.421
Nulliparous	75.203[a]		NR (-)	
Multiparous	NR (-)		51.647[a]	

[a]95% CI cannot be calculated. PFS, progression-free survival; OS, overall survival; CI, confidence interval; BMI, body mass index; NR, not reached.

in previous studies (15,27). The complete response rate in the present study was 34.8%, mainly as the patients underwent optimal surgical debulking and subsequently received adjuvant chemotherapy. A partial response was achieved in 13.0% of the patients and stable disease was achieved in 21.7%.

Numerous studies have shown an increased incidence of KRAS proto-oncogene GTPase and B-Raf proto-oncogene serine/threonine kinase mutations with activation of the MAPK pathway in LGSOC (35,36). MEK inhibitors represent a novel therapeutic approach for patients with recurrent LGSOC. The GOG 281 study reported significantly improved PFS and response rates when using trametinib compared with those when using single-agent chemotherapy (37). Furthermore, selumetinib showed a 15% response rate and a 65% stable disease rate in a phase II study (38).

The limitations of the present study include the retrospective design, long study period and different treatments regarding systemic therapy and surgery (upfront and interval debulking surgery). The retrospective nature of the study was a major limiting factor with regard to sourcing detailed data about the surgical procedure.

The main strengths of the study are the extended follow-up, the pathological review conducted by an expert pathologist in gynecological malignancies and the fact that the surgery was performed by a talented surgeon in a center that sees a high volume of gynecological oncology cases.

In conclusion, LGSOC is a rare type of malignant ovarian cancer, which has a better PFS and OS times than HGSOC as compared with data from the literature. Notably, there is still a lack of precise guidance on the best type of systemic treatment (chemotherapy or hormonal therapy) for LGSOC. In the present study, optimal cytoreduction showed numerically higher, but non-significant, PFS and OS times compared with suboptimal debulking, which is similar to the increased times found in the literature.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HH, MAE and AB conceived the study and wrote the proposal. BA, YS, AJ, AQ, ALSH, AYSH and IM collected the data. HH, MAE, AB, BA, YS, AJ, AQ, ALSH, AYSH, TH and IM analyzed the data. HH, MAE, AB, BA, YS, AJ, AQ, ALSH, AYSH, TH and IM confirm the authenticity of all of the raw data. HH and MAE wrote the first draft of the manuscript. All

authors critically revised the manuscript for important intellectual content, and have read and approved the final version.

Ethics approval and consent to participate

All methods followed the relevant guidelines and regulations. The study was approved, and the requirement for informed patient consent was waived by, the Research Advisory Council at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia; approval no. 2231168).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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