

# Clinical parameters affecting survival outcomes in patients with low-grade serous ovarian carcinoma: an international multicentre analysis

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**Background:** Women with low-grade ovarian serous carcinoma (LGSC) benefit from surgical treatment; however, the role of chemotherapy is controversial. We examined an international database through the Ovarian Cancer Association Consortium to identify factors that affect survival in LGSC.

**Methods:** We performed a retrospective cohort analysis of patients with LGSC who had had primary surgery and had overall survival data available. We performed univariate and multivariate analyses of progression-free survival and overall survival, and generated Kaplan–Meier survival curves.

**Results:** Of the 707 patients with LGSC, 680 (96.2%) had available overall survival data. The patients' median age overall was 54 years. Of the 659 patients with International Federation of Obstetrics and Gynecology stage data, 156 (23.7%) had stage I disease, 64 (9.7%) had stage II, 395 (59.9%) had stage III, and 44 (6.7%) had stage IV. Of the 377 patients with surgical data, 200 (53.0%) had no visible residual disease. Of the 361 patients with chemotherapy data, 330 (91.4%) received first-line platinum-based chemotherapy. The median follow-up duration was 5.0 years. The median progression-free survival and overall survival were 43.2 months and 110.4 months, respectively. Multivariate analysis indicated a statistically significant impact of stage and residual disease on progression-free survival and overall survival. Platinum-based chemotherapy was not associated with a survival advantage.

**Conclusion:** This multicentre analysis indicates that complete surgical cytoreduction to no visible residual disease has the most impact on improved survival in LGSC. This finding could immediately inform and change practice.

**Contexte :** L'efficacité du traitement chirurgical du carcinome séreux de bas grade (CSBG) de l'ovaire est reconnue, mais l'intérêt de la chimiothérapie est controversé. Nous avons cherché à déterminer les facteurs qui influencent la survie au CSBG dans une base de données internationale de l'Ovarian Cancer Association Consortium.

**Méthodes :** Nous avons mené une analyse de cohorte rétrospective de patientes atteintes de CSBG ayant subi une chirurgie initiale. À partir de leurs données de survie globale, nous avons effectué des analyses univariées et multivariées de la survie sans progression et de la survie globale et avons généré des courbes de Kaplan–Meier relatives à la survie.

**Résultats :** Les données de survie globale de 680 (96,2 %) patientes atteintes de CSBG sur 707 (âge médian 54 ans) étaient disponibles. Des 659 patientes pour qui on avait des données sur le stade selon la classification de la Fédération internationale de gynécologie et d'obstétrique, 156 (23,7 %) étaient atteintes d'un cancer de stade I, 64 (9,7 %) de stade II, 395 (59,9 %) de stade III et 44 (6,7 %) de stade IV. Les données chirurgicales de 377 patientes ont permis de déterminer que 200 (53 %) n'avaient aucune maladie résiduelle visible. Des 361 patientes avec des données de chimiothérapie, 330 (91,4 %) avaient reçu une chimiothérapie à base de platine en première intention. Le suivi médian a duré 5 ans, avec une survie sans progression et une survie globale médianes de 43,2 mois et de 110,4 mois, respectivement. Selon l'analyse multivariée, le stade et la maladie résiduelle ont un impact significatif sur la survie sans progression et la survie globale, alors que la chimiothérapie à base de platine n'a été associée à aucun avantage sur la survie.

**Conclusion :** Cette analyse multicentrique indique que la cytoréduction chirurgicale complète, résultant en l'élimination de toute maladie résiduelle, est l'intervention qui améliore le plus la survie au CSBG. Ce résultat peut guider un changement de pratique immédiat.

**E**pithelial ovarian carcinoma has the highest fatality-to-case ratio of all gynecologic malignant disorders.<sup>1,2</sup> The most commonly diagnosed epithelial ovarian cancer is serous carcinoma.<sup>1,2</sup> The MD Anderson Cancer Center and Johns Hopkins 2-tier grading system divides serous carcinoma into low-grade, corresponding to Silverberg grade 1 tumours, and high-grade, corresponding to Silverberg grade 2 and 3 tumours, based on the degree of nuclear atypia.<sup>3–7</sup>

Low-grade serous carcinoma (LGSC) accounts for 10% of all epithelial ovarian malignant tumours.<sup>3–6</sup> Low-grade serous carcinoma has a distinct molecular identity, clinical behaviour and overall survival, as compared to the more common high-grade serous ovarian carcinoma (HGSC); hence, they have been classified as 2 distinct malignant disorders.<sup>6,8</sup> Our group has shown differential gene expression profiles between LGSC and HGSC.<sup>9,10</sup> Low-grade serous carcinoma more frequently exhibits mutations in *KRAS*, *BRAF*, *NRAS* and other genes in the mitogen-activated kinase pathway,<sup>11–13</sup> whereas HGSC harbours near-universal mutations in the p53 pathway.<sup>8,13,14</sup> Clinically, LGSC tumours are slow-growing and may affect younger, premenopausal women.<sup>6,8</sup>

The management of women with LGSC remains challenging given the rarity of this disease and limited therapeutic options. Evidence to date suggests limited benefit of cytotoxic therapy, since these tumours are often resistant to platinum-based chemotherapy and response rates are low.<sup>15</sup> In a 2016 analysis of the AGO Study Group meta-database, Grabowski and colleagues<sup>16</sup> reported a significantly lower response to systemic chemotherapy in

patients with LGSC than in those with HGSC. Similarly, in a series of 25 patients treated with neoadjuvant chemotherapy for advanced-stage LGSC, the response rate was 4%,<sup>17</sup> far below the objective response rate of about 80% often seen in patients with HGSC.<sup>18</sup> Furthermore, Gershenson and colleagues<sup>6</sup> reported that only 52% of patients with LGSC had no evidence of visible residual disease after completing cytoreductive surgery and adjuvant platinum-based chemotherapy.

It is therefore increasingly evident that the empirical “standard” platinum-based chemotherapy approach to treatment of high-grade ovarian carcinoma may not be suitable for LGSC and that novel therapeutic strategies are needed that address the molecular heterogeneity and specific pathogenesis of this rare tumour. Notably, most LGSC tumours overexpress estrogen receptors and, to a lesser extent, progesterone receptors.<sup>19,20</sup> These receptors are being investigated as potential therapeutic targets in several studies.<sup>20,21</sup> In addition to hormone receptors, other actionable mutations that are frequently identified in the mitogen-activated kinase pathway may also serve as possible therapeutic targets in patients with LGSC tumours.<sup>22,23</sup>

In the present study, we examined a large data set of patients diagnosed with LGSC through the Ovarian Cancer Association Consortium (OCAC), a collaborative network formed in 2005 as an international consortium of ovarian cancer investigators with the goal of performing collaborative studies. The primary objective of this analysis was to identify clinical parameters associated with survival outcomes in women with LGSC.

**METHODS**

*Data collection*

We performed a comprehensive retrospective cohort analysis of de-identified clinical data for patients with LGSC from the OCAC database and the Princess Margaret Cancer Centre, Toronto, Ontario, Canada. For OCAC study cases, clinical information was collected at each participating site and centralized into a clinical database (see Appendix 1, Supplemental Table S1, available at [www.canjsurg.ca/lookup/doi/10.1503/cjs.017020/tab-related-content](http://www.canjsurg.ca/lookup/doi/10.1503/cjs.017020/tab-related-content), for the list of contributing OCAC study sites and acronyms). Patients with newly diagnosed primary LGSC were included. All study patients underwent primary surgical resection. All patients had central pathology review, and a pathology report by a specialized gynecologic pathologist confirming the diagnosis of LGSC was required.

Patient demographic characteristics collected included age at diagnosis (continuous), International Federation of Obstetrics and Gynecology (FIGO) stage, residual disease status after primary surgical resection (grouped as visible residual disease v. no visible residual disease for the purpose of our analysis) and first-line platinum-based chemotherapy (any v. none). Year of diagnosis was not provided by OCAC sites but, rather, was determined from age at diagnosis and year of birth. Residual disease status was provided by contributing OCAC sites according to the following categories: 1) no macroscopic disease, 2) macroscopic disease less than 1 cm; 3) macroscopic disease 1–2 cm, 4) macroscopic disease less than 2 cm but no further details, 5) macroscopic disease greater than 2 cm, 6) macroscopic disease of unknown size, 7) tumour not resected, 8) macroscopic disease greater than 1 cm but no further details and 9) unknown. Data collection and sharing were in accordance with the research ethics boards of all study institutions, including University Health Network, Toronto, the primary study site.

*Data analysis*

We calculated progression-free survival from the date of diagnosis to the date of first progression (based on CA-125 level, imaging and clinical criteria) or date of death, as previously described.<sup>24</sup> We calculated overall survival from the date of diagnosis to the date of death; patients who remained alive were censored on the date of last follow-up. We estimated progression-free survival and overall survival using the Kaplan–Meier method. Log-rank tests were used to examine survival differences. We performed univariate and multivariate analyses using Cox proportional hazards modelling. Clinically relevant factors, including age at diagnosis, FIGO stage, residual disease and platinum-based chemotherapy, were included in the model. The statistical

programming software packages used in this study were SAS version 9.3 (SAS Institute) and R version 3.0.0 (R Corporation for Statistical Computing). All tests were 2-sided, and *p* values < 0.05 were considered statistically significant.

**RESULTS**

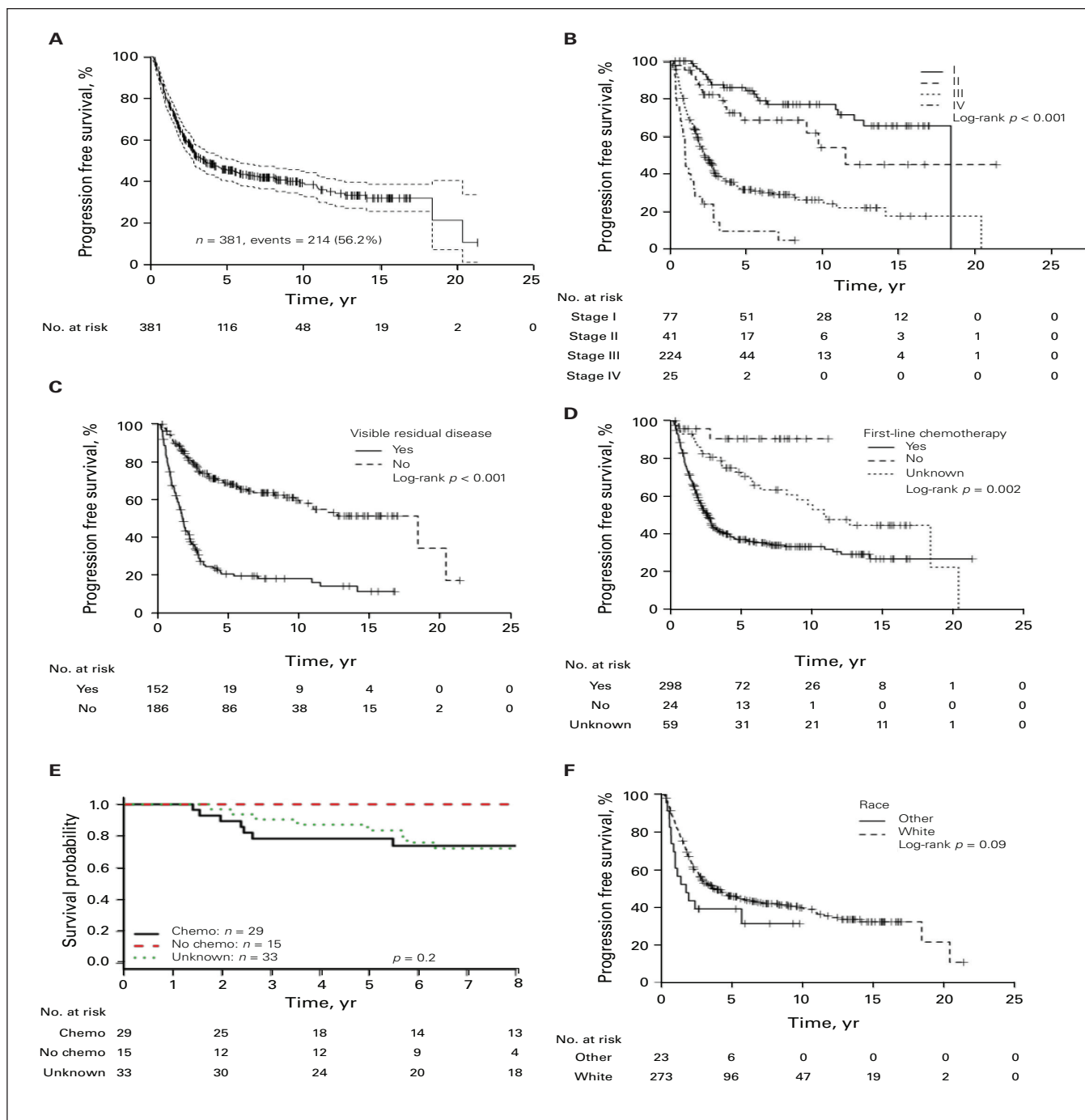
There were 707 patients with LGSC in the combined database, 667 from the OCAC database and 40 from the Princess Margaret Cancer Centre. Patient demographic and clinical characteristics are given in Table 1. The median age at diagnosis was 54 (range 18–85) years. Year of diagnosis ranged from 1986 to 2014 for OCAC study sites and from 1992 to 2015 for Princess Margaret Cancer Centre cases. The majority of patients had advanced FIGO stage disease at diagnosis: of the 659 patients (93.2%) with stage information available, 156 (23.7%) had stage I disease, 64 (9.7%) had stage II disease, 395 (59.9%) had stage III disease, and 44 (6.7%) had stage IV disease.

Information on residual disease after cytoreductive surgery was available for 377 patients (53.3%), of whom 200 (53.0%) had no visible residual disease at the conclusion of surgery and 177 (47.0%) had visible residual disease. Chemotherapy data were available for 361 patients (51.1%), of whom 330 (91.4%) were treated with first-line platinum-based chemotherapy and 31 (8.6%) did not receive primary chemotherapy.

**Table 1. Demographic and clinical characteristics of women diagnosed with low-grade serous carcinoma in the Ovarian Cancer Association Consortium cohort**

Characteristic	No. (%) of women <i>n</i> = 707
Age at diagnosis, yr	
Mean ± SD	54.2 ± 13.7
Median (range)	54 (18–85)
FIGO stage ( <i>n</i> = 659)	
I	156 (23.7)
II	64 (9.7)
III	395 (59.9)
IV	44 (6.7)
Residual disease after cytoreductive surgery ( <i>n</i> = 391)	
No visible disease/complete microscopic resection	200 (51.2)
Any visible residual disease†	177 (45.3)
Tumour not resected (e.g., inoperable, biopsy only)	14 (3.6)
Received first-line platinum-based chemotherapy ( <i>n</i> = 361)	
Yes	330 (91.4)
No	31 (8.6)

FIGO = International Federation of Obstetrics and Gynecology; SD = standard deviation.  
 \*Based on information available for each variable.  
 †Except where noted otherwise.  
 ‡Less than 1 cm: *n* = 65; 1–2 cm: *n* = 1; less than 2 cm with no further details: *n* = 12; greater than 2 cm: *n* = 23; greater than 1 cm with no further details: *n* = 2; size unknown: *n* = 74.



**Fig. 1.** Kaplan-Meier progression-free survival estimates (A) overall, (B) stratified by International Federation of Obstetrics and Gynecology (FIGO) stage, (C) stratified by residual disease after cytoreductive surgery, (D) stratified by treatment with platinum-based chemotherapy (chemo), (E) stratified by treatment with platinum-based chemotherapy in patients with stage I disease and (F) stratified by race.

*Progression-free survival*

In all, 381 patients (53.9%) had complete data on progression-free survival. The median duration of follow-up was 5.0 (range 0.01–31.9) years. The median progression-free survival was 43.2 months. The 3-year progression-free survival probability was 52% (95% confidence interval [CI

47%–58%), and the 5-year progression-free survival probability was 45% (95% CI 40%–51%) (Figure 1A). Multivariate analysis controlling for age, stage and residual disease indicated a statistically significant difference in progression-free survival related to stage and residual disease (Table 2 and Figure 1B and C). The hazard ratio (HR) for the comparison between stage III versus stage I disease was 2.67

**Table 2. Results of univariate and multivariate analysis of progression-free survival**

Variable	Univariate*		Multivariate†	
	HR	p value	HR	p value
Age (continuous)	1.16 (1.04–1.29)	0.006	1.18 (1.03–1.34)	0.02
Stage	—	< 0.001	—	< 0.001
II v. I	1.58 (0.80–3.14)	0.2	1.39 (0.68–2.88)	0.4
III v. I	4.92 (3.06–7.91)	< 0.001	2.67 (1.50–4.76)	< 0.001
IV v. I	11.40 (6.16–21.01)	< 0.001	3.98 (1.80–8.81)	< 0.001
Residual disease (any v. none visible)	3.88 (2.85–5.28)	< 0.001	2.42 (1.65–3.57)	< 0.001
Platinum-based chemotherapy	—	0.002	—	—
Any v. none	9.87 (2.45–39.77)	0.001	—	—
Unknown v. none	4.75 (1.13–19.96)	0.03	—	—
Race (White v. other)	0.63 (0.37–1.07)	0.09	0.68 (0.38–1.24)	0.2

HR = hazard ratio.  
 \*Number of complete observations: age 381, stage 367, residual disease 338, platinum-based primary chemotherapy 381, race 296.  
 †Number of complete observations: 333.

(95% CI 1.50–4.76), and between stage IV versus stage I disease, 3.98 (95% CI 1.80–8.81). The 5-year progression-free survival probability by stage was as follows: stage I 84% (95% CI 76%–93%), stage II 69% (95% CI 54%–86%), stage III 32% (95% CI 26%–39%) and stage IV 10% (95% CI 3%–35%). Multivariate analysis of residual disease showed an HR of 2.42 (95% CI 1.65–3.57) for any versus none visible. First-line platinum-based treatment was associated with an increased risk for progression in the full cohort on univariate analysis (any v. none: HR 9.87, 95% CI 2.45–39.77) (Table 2 and Figure 1D). However, treatment status was significantly correlated to both FIGO stage (Appendix 1, Supplemental Table S2) and residual disease (Appendix 1, Supplemental Table S3); hence, chemotherapy was not included in the multivariate analysis for progression-free survival or overall survival. No significant association between chemotherapy and progression-free survival was observed when the analysis was limited to stage I disease ( $p = 0.2$ ) (Figure 1E). Race was also not significantly associated with progression-free survival (White v. other: HR 0.68, 95% CI 0.38–1.24) (Table 2 and Figure 1F).

### Overall survival

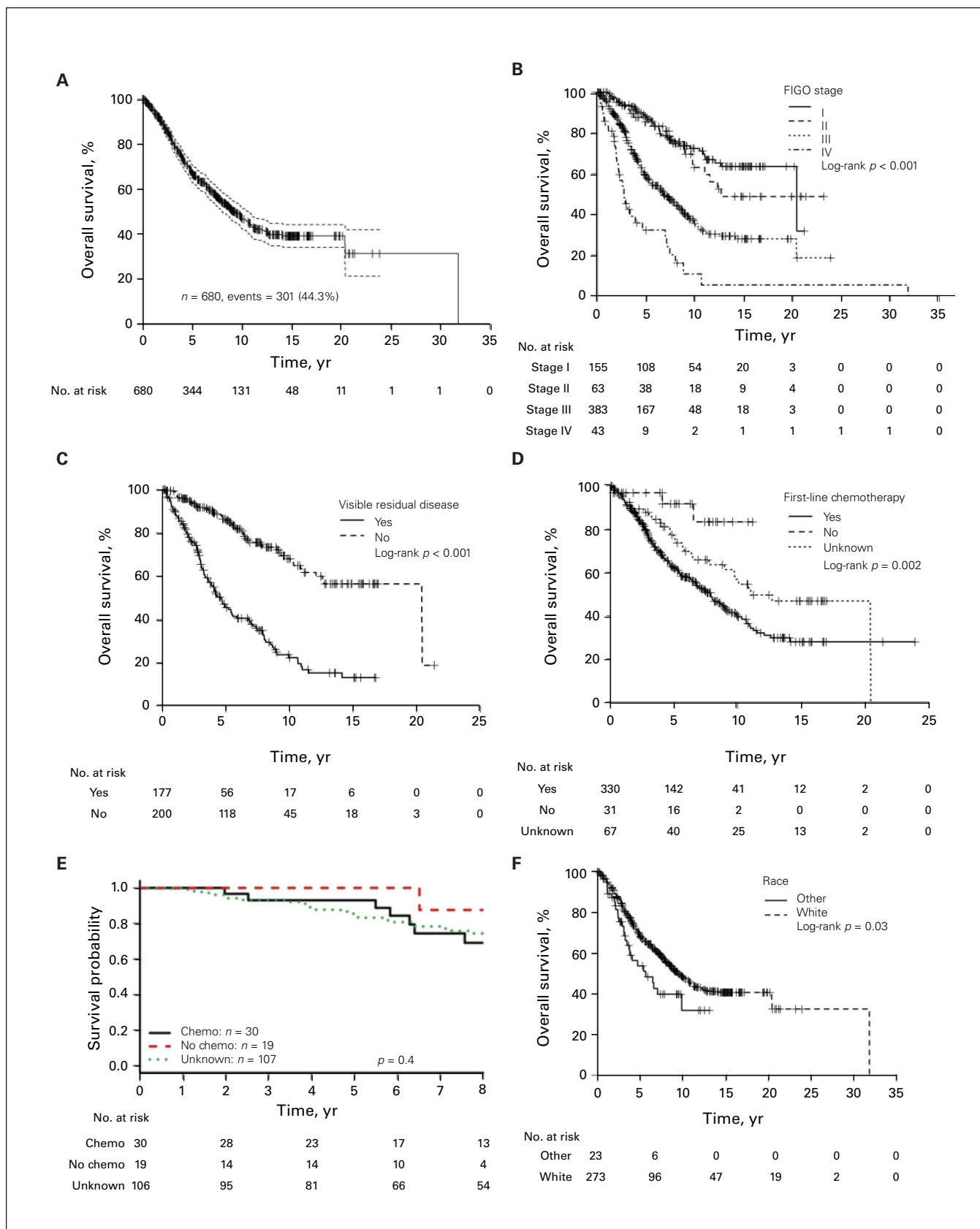
Of the 707 patients, 680 (96.2%) (640 OCAC cases and 40 Princess Margaret Cancer Centre cases) had available overall survival data and were included in the final analysis. The median overall survival was 110.4 months. The 3-year overall survival probability was 81% (95% CI 78%–84%), and the 5-year overall survival probability was 67% (95% CI 63%–71%) in the full cohort (Figure 2A). Overall survival was significantly associated with stage (stage III v. stage I: HR 2.00, 95% CI 1.09–3.66; stage IV v. stage I: HR 3.61, 95% CI 1.66–7.85) and residual disease (any v. none visible: HR 2.53, 95% CI 1.65–3.90) (Table 3 and Figure 2B and C). The 5-year overall survival probability by stage was as follows: stage I 88% (95% CI 82–93),

stage II 83% (95% CI 74–94), stage III 58% (95% CI 53–64) and stage IV 32% (95% CI 20–53). First-line platinum-based treatment was not associated with an overall survival advantage in stage I disease ( $p = 0.4$ ) (Figure 2E). Race was found to have a modest impact on overall survival on multivariate analysis (White v. other: HR 0.51, 95% CI 0.28–0.92) (Table 3 and Figure 1F).

### DISCUSSION

In this analysis, we examined the clinical outcomes of a large number of patients with well-characterized and carefully annotated LGSC tumours using a collaborative database. Importantly, FIGO stage was found to be an independent poor prognostic factor, with stage III and IV disease being associated with shorter survival. Furthermore, women derived a significant survival benefit from complete cytoreductive surgery (HR 2.53 in patients with visible residual disease v. none visible). These results corroborate those of previous studies in LGSC and confirm the strong association between complete surgical resection and no residual disease and survival, indicating that surgery should remain the cornerstone in the management algorithm of women with LGSC.<sup>25–27</sup> Given the limited systemic options in this patient population, we believe all patients should undergo surgery performed by gynecologic oncologists with an attempt at complete resection to no visible residual disease.

Similarly, in an ancillary analysis of Gynecologic Oncology Group (GOG) protocol 182 in 189 women with ovarian LGSC, Nickles Fader and colleagues<sup>27</sup> showed that patients with no residual disease had the best survival outcomes. Notably, in that analysis, patients with any residual disease, whether it was classified as optimal (1–9 mm) or suboptimal ( $\geq 10$  mm), had equivalent survival durations that were significantly worse than that of patients with no visible residual disease. This finding is in



**Fig. 2.** Kaplan-Meier overall survival estimates (A) overall, (B) stratified by International Federation of Obstetrics and Gynecology (FIGO) stage, (C) stratified by residual disease after cytoreductive surgery, (D) stratified by treatment with platinum-based chemotherapy (chemo), (E) stratified by treatment with platinum-based chemotherapy in patients with stage I disease and (F) stratified by race.

Table 3. Results of univariate and multivariate analysis of overall survival

Variable	Univariate*		Multivariate†	
	HR	p value	HR	p value
Age (continuous)	1.28 (1.18–1.40)	< 0.001	1.25 (1.10–1.43)	0.001
Stage	—	< 0.001	—	0.003
II v. I	1.28 (0.75–2.19)	0.4	1.05 (0.49–2.24)	0.9
III v. I	3.02 (2.14–4.24)	< 0.001	2.00 (1.09–3.66)	0.02
IV v. I	7.18 (4.46–11.54)	< 0.001	3.61 (1.66–7.85)	0.001
Residual disease (any v. none visible)	3.98 (2.83–5.58)	< 0.001	2.53 (1.65–3.90)	< 0.001
Platinum-based chemotherapy	—	0.002	—	—
Any v. none	4.59 (1.46–14.4)	0.009	—	—
Unknown v. none	2.93 (0.89–9.63)	0.08	—	—
Race (White v. other)	0.65 (0.44–0.96)	0.03	0.51 (0.28–0.92)	0.02

HR = hazard ratio.  
 \*Number of complete observations: age 680, stage 644, residual disease 377, platinum-based primary chemotherapy 428, race 575.  
 †Number of complete observations: 284.

contrast to patients with HGSC, in whom residual disease of 1–9 mm has a survival advantage compared to suboptimal residual resection ( $\geq 10$  mm residual disease).<sup>28–32</sup> Interestingly, complete resection was achieved in only about 25% of patients with LGSC and 25% of those with HGSC in the GOG protocol 182 cohort.<sup>27</sup> Similar resection outcomes were achieved in LGSC and HGSC despite the fact that patients with LGSC had more favourable surgical factors, including lower preoperative CA-125 levels and less ascites, than patients with HGSC. A potential explanation is that when the GOG protocol 182 was conducted, the surgical goal was to achieve optimal resection, not microscopic resection. As such, the surgeon may not have attempted complete resection to no visible residual disease once optimal resection to 1–9 mm was achieved. The paradigm shift in ovarian cancer surgery with the goal of achieving microscopic resection occurred after the GOG protocol 182 concluded.<sup>28–33</sup> Our data indicate that resection to no residual disease is crucial in patients with LGSC. Although tumour biology may play a role in disease distribution and the feasibility of resection, it is not a modifiable factor. We therefore advocate that commitment to complete surgical cytoreduction should be an essential part of the management strategy of this disease. Maximal surgical efforts should be attempted when feasible and may include multivisceral resection and a multidisciplinary surgical approach with the goal of achieving complete resection to no visible residual disease.

The role of adjuvant systemic chemotherapy in LGSC is less clear and remains controversial. Our data show that patients treated with primary platinum-based chemotherapy did not experience improved survival outcomes if cytotoxic chemotherapy was administered. The role of chemotherapy in this setting was studied in 280 patients with advanced LGSC through the National Cancer Database.<sup>34</sup> In that analysis, no survival benefit was observed

with standard chemotherapy: overall survival was 88.2 months in patients who received systemic chemotherapy, compared to 95.9 months in a propensity score-matched cohort who were not treated with chemotherapy. Moreover, when limited to patients with stage I disease, treatment with postoperative chemotherapy did not improve survival outcomes. In a recent retrospective multicentre analysis of 134 Canadian women with LGSC who were treated with a combination of surgery and systemic chemotherapy, the median progression-free survival was 22.6 months and the median overall survival 39.4 months in patients with stage II–IV disease.<sup>35</sup> Importantly, 27% of patients were treated with neoadjuvant chemotherapy, and only 31% had complete cytoreductive surgery. These factors may have contributed to the relatively low survival outcomes.

Given the relative chemoresistance of LGSC tumours, hormone-based therapy and targeted therapies, mainly to the mitogen-activated kinase pathway, are actively being considered in these patients, both in clinical practice and in the research setting.<sup>20–23</sup> Overexpression of estrogen receptors and overexpression of progesterone receptors in LGSC have been studied as potential therapeutic targets.<sup>20,21</sup> The National Comprehensive Cancer Network guidelines list antihormonal therapy using aromatase inhibitors, tamoxifen or leuprolide acetate as valid therapeutic options for women with LGSC in either the upfront or recurrent setting.<sup>25</sup> In a study of 27 patients with stage II–IV LGSC, Fader and colleagues<sup>20</sup> reported that treatment with surgical resection followed by hormonal therapy was associated with median progression-free survival of 22 months and a recurrence rate of 14.8%. The rates of 3-year progression-free survival and overall survival were 79.0% and 92.6%, respectively. These findings were not significantly different from those for an age- and stage-matched control group of patients with LGSC treated with surgery and adjuvant chemotherapy. Those

authors concluded that chemotherapy may not be necessary in patients with advanced-stage disease who undergo an attempt at maximal cytoreductive surgery and receive adjuvant hormonal therapy after surgery.

In addition, Gershenson and colleagues<sup>21</sup> examined the role of maintenance antihormone treatment in a retrospective review. Significantly, patients treated with maintenance hormonal therapy had better progression-free survival than patients who did not receive maintenance therapy (64.9 mo v. 27.3 mo,  $p < 0.001$ ). Hormonal therapy may play a role in the management of patients with LGSC, both in the adjuvant therapeutic phase and the maintenance setting. An international cooperative group randomized controlled trial comparing chemotherapy and maintenance hormonal therapy with hormonal therapy alone after primary cytoreductive surgery in women with advanced-stage LGSC is planned.

The mitogen-activated kinase pathway is an attractive treatment target; however, specific therapeutics have not yet been integrated into clinical practice. Molecular studies have shown that LGSC frequently exhibits *KRAS*, *NRAS*, *BRAF*, *PTEN* and *CTNNB1* mutations and rarely harbours *TP53* mutations.<sup>11–13</sup> During tumour progression, LGSC neoplasms appear to acquire increasing genetic abnormalities such as loss of chromosome 5q, which is associated with malignant transformation, and loss of chromosome 1p, which is associated with the acquisition of invasive phenotypes.<sup>35</sup> Farley and colleagues<sup>22</sup> studied the MEK 1/2 inhibitor selumetinib in a single-arm phase II protocol (GOG protocol 239) in patients with recurrent LGSC. They found that selumetinib was well tolerated and had a response rate of 15% and a disease control rate of 63% in recurrent LGSC. The MEK inhibitor in low-grade serous ovarian cancer (MILO) phase III randomized trial was designed to investigate the role of the potent MEK inhibitor binimetinib versus standard chemotherapy in patients with recurrent or persistent LGSC.<sup>23</sup> In contrast to GOG protocol 239, this study was terminated prematurely after a planned interim analysis showed that the HR for progression-free survival crossed the predefined futility boundary. The authors recently presented results of the MILO study.<sup>36</sup> A total of 303 patients were randomly allocated in a 2:1 ratio to binimetinib (201 patients) or physician's choice chemotherapy (102 patients). The median progression-free survival was 9.1 months in the binimetinib arm and 10.6 months in the physician's choice chemotherapy arm (HR 1.21, 95% CI 0.79–1.86). The median overall survival was 25.3 months for binimetinib and 20.8 months for physician's choice chemotherapy. Interestingly, a post hoc analysis suggested potential correlation between *KRAS* mutation and tumour response to binimetinib. Therefore, the role of MEK-based combination therapy in patients with LGSC warrants additional investigation, particularly in the subgroup with *KRAS*/*NRAS* mutations.

## Limitations

Strengths of this work include the large number of patients analyzed. This is of particular importance in LGSC as it is a rare tumour, and most single-institution databases have limited number of patients with this disease. The pathology diagnosis in this cohort was reported by specialized gynecologic pathologists for diagnostic accuracy of this challenging tumour subtype. In addition, this study represents a collaborative initiative across multiple international leading cancer centres. Weaknesses of our study include its retrospective nature and the inherent limitations associated with this study design. Data were retrieved from a multi-institutional cohort with potential variations in data entry and result interpretations. Moreover, data were incomplete for some patients in several metrics.

## CONCLUSION

This multicentre analysis shows that surgical resection to no visible residual disease has significant impact on survival of patients with LGSC, and this could immediately inform and change practice. In contrast, platinum-based chemotherapy was not associated with improved survival in this patient cohort. It is important to further analyze the study cohort to understand whether there are variations in treatment response among patients with LGSC, as some patients show clinical benefit to systemic chemotherapy. We plan to conduct additional subgroup analyses of patients with differential response to systemic therapies to identify potential subgroups that are more likely to derive clinical benefit. In addition, genotyping and targeted sequencing of LGSC cases are underway to examine genomic alterations that may predict response to systemic therapies and may also help uncover novel actionable mutations.

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