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

Taymaa May, MD, MSc[; Marcus Bernardini, MD, MSc; Stephanie Lheureux, MD, PhD; Katja K.H. Aben, PhD; Elisa V. Bandera, PhD; Matthias W. Beckmann, MD; Javier Benitez, MD; Andrew Berchuck, MD; Line Bjørge, MD, PhD; Michael E. Carney, PhD; Daniel W. Cramer, MD; Anna deFazio, PhD; Thilo Dörk, PhD; Diana M. Eccles, MD; Michael Friedlander, PhD; María Jose García, PhD; Ellen L. Goode, PhD; Alexander Hein, MD; Claus K. Høgdall, MD; Allan Jensen, PhD; Sharon Johnatty, PhD; Catherine J. Kennedy, PhD; Lambertus A. Kiemeney, PhD; Susanne K. Kjær, MD; Jolanta Kupryjańczyk, MD, PhD; Keitaro Matsuo, MD, PhD; Valerie McGuire, PhD; Francesmary Modugno, PhD; Lisa E. Paddock, PhD; Tanja Pejovic, MD, PhD; Catherine M. Phelan, MD, PhD; Marjorie J. Riggan, BSc; Cristina Rodriguez-Antona, PhD; Joseph H. Rothstein, MD; Weiva Sieh, MD, PhD; Honglin Song, PhD; Kathryn L. Terry, ScD; Anne M. van Altena, PhD; Adriaan Vanderstichele, PhD; Ignace Vergote, MD, PhD; Liv Cecilie Vestrheim Thomsen, MD; Penelope M. Webb, PhD; Nicolas Wentzensen, MD, PhD; Lynne R. Wilkens, PhD; Argyrios Ziogas, PhD; Haiyan Jiang, MSc; Alicia Tone, PhD; on behalf of the Ovarian Cancer Association and the Australian Ovarian Cancer Study Group

Accepted May 25, 2021

Correspondence to:
T. May
Princess Margaret Cancer Centre
OPG Wing 6-811, 610 University Ave
Toronto ON M5G 2M9
Taymaa.May@uhn.ca

Cite as: *Can J Surg* 2023 June 27;66(3). doi: 10.1503/cjs.017020

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.

Epithelial ovarian carcinoma has the highest fatality-to-case ratio of all gynecologic malignant disorders.[1,2] The most commonly diagnosed epithelial ovarian cancer is serous carcinoma.[1,2] 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.[3–7]

Low-grade serous carcinoma (LGSC) accounts for 10% of all epithelial ovarian malignant tumours.[3–6] 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.[6,8] Our group has shown differential gene expression profiles between LGSC and HGSC.[9,10] Low-grade serous carcinoma more frequently exhibits mutations in *KRAS*, *BRAF*, *NRAS* and other genes in the mitogen-activated kinase pathway,[11–13] whereas HGSC harbours near-universal mutations in the p53 pathway.[8,13,14] Clinically, LGSC tumours are slow-growing and may affect younger, premenopausal women.[6,8]

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.[15] In a 2016 analysis of the AGO Study Group meta-database, Grabowski and colleagues[16] 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%,[17] far below the objective response rate of about 80% often seen in patients with HGSC.[18] Furthermore, Gershenson and colleagues[6] 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.[19,20] These receptors are being investigated as potential therapeutic targets in several studies.[20,21] 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.[22,23]

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, 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.[24] 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† n = 707
Age at diagnosis, yr	
Mean ± SD	54.2 ± 13.7
Median (range)	54 (18–85)
FIGO stage (n = 659)	
I	156 (23.7)
II	64 (9.7)
III	395 (59.9)
IV	44 (6.7)
Residual disease after cytoreductive surgery (n = 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 (n = 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.

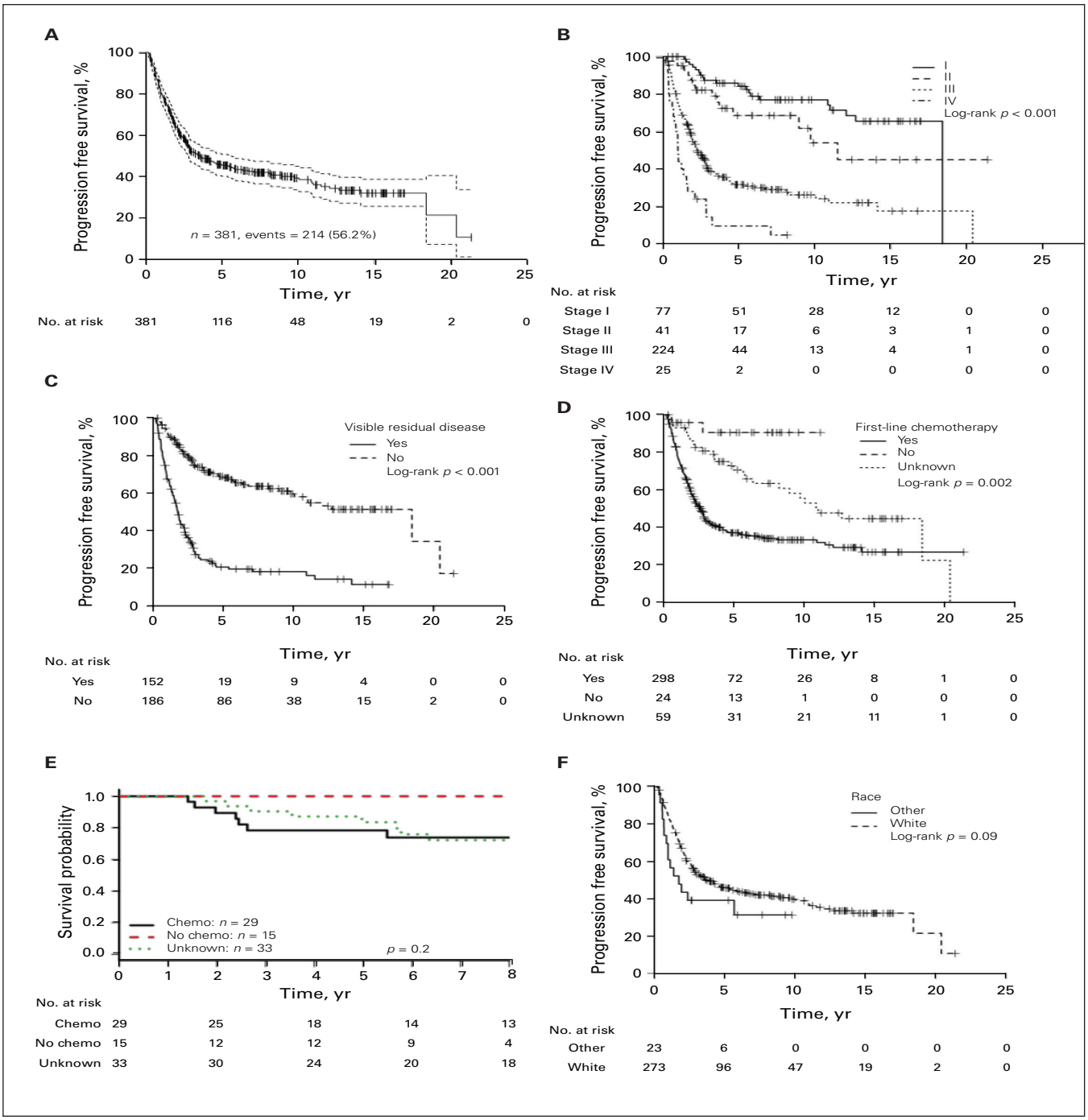

Fig. 1. Kaplan–Meier progression-free survival estimates (A) overall, (B) stratified by International Federation of Obstetrics and Gynecology (FIGO) stage, (C) stratified by residual disease after cytoreductive surgery, (D) stratified by treatment with platinum-based chemotherapy (chemo), (E) stratified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

	Univariate*		Multivariate†	
Variable	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.[25–27] 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[27] 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 (≥ 10 mm), had equivalent survival durations that were significantly worse than that of patients with no visible residual disease. This finding is in

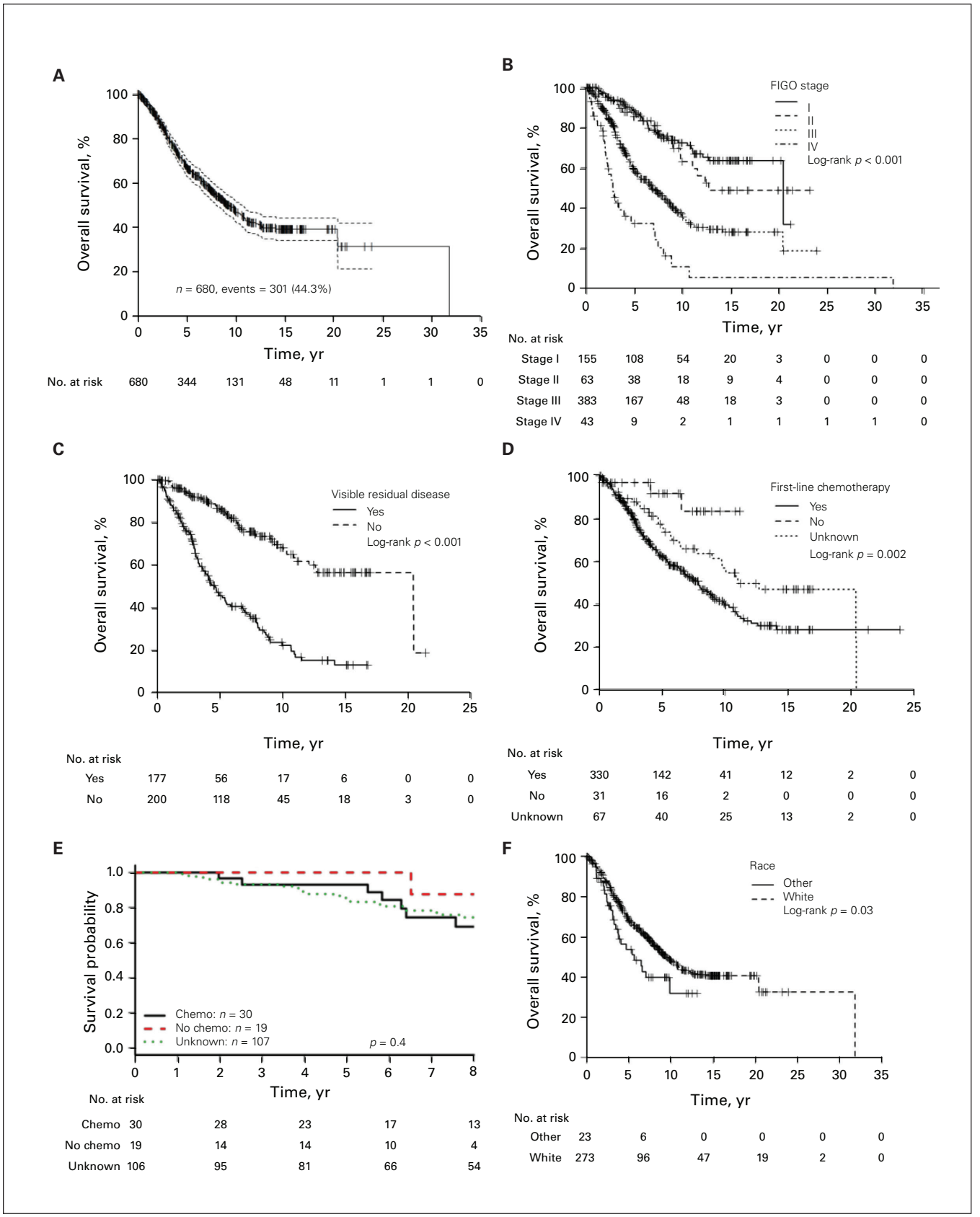

Fig. 2. Kaplan–Meier overall survival estimates (A) overall, (B) stratified by International Federation of Obstetrics and Gynecology (FIGO) stage, (C) stratified by residual disease after cytoreductive surgery, (D) stratified by treatment with platinum-based chemotherapy (chemo), (E) stratified by treatment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

	Univariate*		Multivariate†	
Variable	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 (≥ 10 mm residual disease).[28–32] 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.[27] 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.[28–33] 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.[34] 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.[35] 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.[20–23] Overexpression of estrogen receptors and overexpression of progesterone receptors in LGSC have been studied as potential therapeutic targets.[20,21] 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.[25] In a study of 27 patients with stage II–IV LGSC, Fader and colleagues[20] 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[21] 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.[11–13] 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.[35] Farley and colleagues[22] 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.[23] 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.[36] 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.

Acknowledgments: Acknowledgements for individual studies: AUS: the Australian Ovarian Cancer Study (AOCS) acknowledges the cooperation of the participating institutions in Australia, as well as the contributions of the study nurses and research assistants, and all clinical and scientific collaborators to the study. The complete AOCS Study Group can be found at www.aocstudy.org. The AOCS thanks all of the women who participated in these research programs. MOF: The investigators thank the Total Cancer Care Protocol and the Collaborative Data Services and Tissue Core Facilities at the H. Lee Moffitt Cancer Center & Research Institute, a National Cancer Institute–designated Comprehensive Cancer Center (P30-CA076292), and the state of Florida. OPL: The investigators thank the members of the Ovarian cancer Prognosis And Lifestyle (OPAL) Study Group (http://opalstudy.qimrberghofer.edu.au/). SRO: The investigators thank all members of the Scottish Gynaecological Clinical Trials group and the Scottish Randomized Trial in Ovarian Cancer 1 (SCOTROC1) investigators. UHN: The investigators thank the Princess Margaret Cancer Centre Foundation – Bridge for the Cure. WMH: The investigators thank the Gynaecological Oncology Biobank at Westmead, a member of the Australasian Biospecimen Network – Oncology group.

Affiliations: From the Division of Gynecologic Oncology, University Health Network, Princess Margaret Cancer Centre, Toronto, Ont. (May, Bernardini, Tone); the Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ont. (May, Bernardini); the Division of Medical Oncology, Department of Medicine, Princess

Margaret Cancer Centre, Toronto, Ont. (Lheureux); the Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Australia (Johnatty); the Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia (Webb); the Department of Medical Oncology, Prince of Wales Hospital, Sydney, Australia (Friedlander); the Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen Nuremberg, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany (Beckmann, Hein); the Division of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, Calif. (Fasching); the Division of Gynecologic Oncology, Department of Obstetrics and Gynaecology and Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium (Vanderstichele, Vergote); the Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain (Benitez, García, Rodriguez-Antona); the Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain (Benitez, García, Rodriguez-Antona); the Department of Obstetrics and Gynecology, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii (Carney); the Gynaecology Research Unit, Hannover Medical School, Hanover, Germany (Dörk); the Women's Cancer Research Center, Magee-Womens Research Institute and Hillman Cancer Center, Pittsburgh, Penn. (Modugno); the Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Penn. (Modugno); the Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan (Matsuo); the Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan (Matsuo); the Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark (Jensen, Kjær); the Department of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (Kjær); the Department of Health Sciences Research, Mayo Clinic, Rochester, Minn. (Goode); the Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii (Wilkens); the Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Fla. (Phelan); the Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC (Berchuck, Riggan); the Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, Mass. (Cramer, Terry); the Harvard T.H. Chan School of Public Health, Boston, Mass. (Cramer, Terry); the Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ (Bandera); the New Jersey Department of Health and Senior Services, Mercerville, NJ (Paddock); the School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, NJ (Paddock); the Department of Gynecology and Obstetrics, Haukeland University Horpital, Bergen, Norway (Bjørge, Vestrheim Thomsen); the Centre for Cancer Biomarkers CCBIO, Department of Clinical Science, University of Bergen, Bergen, Norway (Bjørge, Vestrheim Thomsen); the Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands (Aben, Kiemeney); the Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands (Aben); the Department of Gynaecology, Radboud University Medical Center, Nijmegen, The Netherlands (van Altena); the Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Ore. (Pejovic); the Knight Cancer Institute, Oregon Health & Science University, Portland, Ore. (Pejovic); the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Md. (Wentzensen); The Juliane Marie Centre, Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (C. Høgdall); the Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK (Song); the Cancer Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK (Eccles); the Department of Health Research and Policy – Epidemiology, Stanford University School of Medicine, Stanford, Calif. (McGuire); the Department of Genetics and Genomic Sciences, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY (Rothstein, Sieh); the Department of Epidemiology, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, Calif. (Ziogas); the Centre for Cancer Research, The Westmead Institute for Medical Research, The University of Sydney, Sydney, Australia (deFazio, Kennedy); the Department of Gynaecological Oncology, Westmead Hospital, Sydney, Australia (deFazio, Kennedy); the Department of Pathology and Laboratory Diagnostics, the Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland (Kupryjanczyk); and the Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, Ont. (Jiang).

Competing interests: Stephanie Lheureux reports study grants from AstraZeneca, GSK and Roche, consulting fees from AstraZeneca, GSK, Roche, Novartis, Merck, Eisai Co. and Shattuck Labs, and speaker's honororia from AstraZeneca, GSK, Eisai Co. and Merck. Line Bjørge is president of the Nordic Society of Gynaecological Oncology executive board. Anna deFazio sits on the Australia New Zealand Gynaecological Oncology Group (ANZGOG) Research Advisory Committee, the Clinical and Scientific Expert Advisory Panel of Ovarian Cancer Australia and the Scientific Advisory Committee of the Australian Gynaecological Cancer Foundation. She is chair of the Translational ANZGOG (TR-ANZGOG) Steering Committee, chair of the International Consortium for Low-Grade Serous Ovarian Cancer Steering Committee and chair of the ANZGOG Translational subcommittee. Michael Friedlander reports consulting fees from AstraZeneca, GSK, MSD, Eli Lilly and Company, Takeda and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, GSK and ACT Genomics; and support for attending meetings and/or travel from AstraZeneca. He sits on the Australasian Gastrointestinal Trial Group independent data monitoring committee and is a Steering Committee member for Abbvie's VELIA trial. Catherine Kennedy is a member of the International Society for Biological and Environmental Repositories Science Policy Committee and of the Australasian Biospecimen Network (ABNA) Management Committee. She is past president and treasurer of ABNA. Liv Cecilie Vestrheim Thomsen reports grants from AstraZeneca, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer and AstraZeneca. She sits on an advisory board for Eisai Co. Ignace Vergote reports consulting fees from Deciphera Pharmaceuticals, Jazz Pharmaceuticals and Oncoinvent AS, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Agenus, AkseBio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai Co., F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Jazz Pharmaceuticals, Karyopharm Therapeutics, MSD, Novocure, Novartis, Oncoinvent AS, Seagen and Sotio Biotech. He sits on a data safety monitoring board or advisory board for Agenus, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai Co., F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, MSD, Novocure, Novartis, Seagen and Sotio Biotech. Penelope Webb reports a speaker's honorarium from AstraZeneca. No other competing interests were declared.

Contributors: T. May and S. Lheureux designed the study. M. Bernardini, K. Aben, E. Bandera, M. Beckmann, J. Benitez, L. Bjørge, M. Carney, D. Cramer, A. deFazio, T. Dörk, D. Eccles, M. Friedlander, M. García, E. Goode, A. Hein, A. Jensen, S. Johnatty, C. Kennedy, L. Kiemeney, S. Kjær, J. Kupryjanczyk, K. Matsuo, V. McGuire, L. Paddock, T. Pejovic, C. Phelan, M. Riggan, C. Rodriguez-Antona, J. Rothstein, H. Song, A. van Altena, L.C. Vestrheim Thomsen, A. Vanderstichele, I. Vergote, P. Webb, L. Wilkens and A. Ziogas acquired the data, which A. Tone, E. Bandera, A. Berchuck, C. Høgdall, F. Modugno, W. Sieh, K. Terry, I. Vergote and N. Wentzensen analyzed. T. May, A. Tone and I. Vergote wrote the manuscript, which M. Bernardini, S. Lheureux, K. Aben, E. Bandera, M. Beckmann, J. Benitez, A. Berchuck, L. Bjørge, M. Carney, D. Cramer, A. deFazio, T. Dörk, D. Eccles, M. Friedlander, M. García, E. Goode, A. Hein, C. Høgdall, A. Jensen, S. Johnatty, C. Kennedy, L. Kiemeney, S. Kjær, Jolanta Kupryjanczyk K. Matsuo, V. McGuire, F. Modugno, L. Paddock, T. Pejovic, C. Phelan, M. Riggan, C. Rodriguez-Antona, J. Rothstein, W. Sieh, H. Song, K. Terry, L.C. Vestrheim Thomsen, A. van Altena, A. Vanderstichele, I. Vergote, P. Webb, N. Wentzensen, L. Wilkens and A. Ziogas critically revised. All authors gave final approval of the article to be published.

Funding: The Ovarian Cancer Association Consortium is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith (PPD/RPCI.07).

Funding for individual studies: AUS: the Australian Ovarian Cancer Study Group was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-01-1-0729, the National Health and Medical Research Council of Australia (APP199600, APP400413 and APP400281), Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania, and Cancer Foundation of Western Australia (Multi-State Applications 191, 211 and 182). The Australian Ovarian Cancer Study gratefully acknowledges additional support from Ovarian Cancer Action (UK), Ovarian Cancer Australia and the Peter MacCallum Foundation. BAV: ELAN Funds of the University of Erlangen-Nuremberg. BEL: National Kankerplan. CNI: Instituto de Salud Carlos III (PI 12/01319) and Ministerio de Economía y Competitividad (SAF2012). GER: German Federal Ministry of Education and Research, Programme of Clinical Biomedical Research (01 GB 9401) and the German Cancer Research Center (DKFZ). HAW: U.S. National Institutes of Health (R01-CA58598, N01-CN-55424 and N01-PC-67001). HJO: Intramural funding and the Rudolf-Bartling Foundation; HOP: Department of Defense (DAMD17-02-1-0669) and National Cancer Institute (K07-CA080668, R01-CA95023, P50-CA159981, MO1-RR000056 and R01-CA126841). JPN: Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare. KRA: This study was partially supported by grant HI16C1127; 0920010 from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea. LAX: American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN) and the National Center for Advancing Translational Sciences (grant UL1TR000124). MAC: National Institutes of Health (R01-CA122443, P30-CA15083 and P50-CA136393), Mayo Foundation, Minnesota Ovarian Cancer Alliance, Fred C. and Katherine B. Andersen Foundation and Fraternal Order of Eagles. MAL: funding for this study was provided by research grant R01-CA61107 from the National Cancer Institute, research grant 94 222 52 from the Danish Cancer Society and the Mermaid I project. MAY: National Institutes of Health (R01-CA122443, P30-CA15083 and P50-CA136393), Mayo Foundation, Minnesota Ovarian Cancer Alliance and Fred C. and Katherine B. Andersen Foundation. MOF: H. Lee Moffitt Cancer Center & Research Institute, Merck Pharmaceuticals, the state of Florida, Hillsborough County and the city of Tampa. NCO: National Institutes of Health (R01-CA76016) and Department of Defense (DAMD17-02-1-0666). NEC: National Institutes of Health (R01-CA54419 and P50-CA105009) and Department of Defense (W81XWH-10-1-02802). NJO: National Cancer Institute (NIH-K07 CA095666, R01-CA83918, NIH-K22-CA138563 and P30-CA072720) and Cancer Institute of New Jersey. NOR: Helse Vest, The Norwegian Cancer Society, The Research Council of Norway. NTH: Radboud University Medical Centre. OPL: National Health and Medical Research Council of Australia (APP1025142) and Brisbane Women's Club. ORE: OHSU Foundation. POL: Intramural Research Program of the National Cancer Institute. PVD: Canadian Cancer Society and Cancer Research Society GRePEC Program. RBH: National Health and Medical Research Council of Australia. SIS: The Sister Study (SISTER) is supported by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health (grants Z01-ES044005 and Z01-ES049033). SRO: Cancer Research UK (C536/A13086, C536/A6689) and Imperial Experimental Cancer Research Centre (C1312/A15589). STA: National Institutes of Health (grants U01 CA71966 and U01 CA69417). TBO: National Institutes of Health (R01-CA106414-A2), American Cancer Society (CRTG-00-196-01-CCE), Department of Defense (DAMD17-98-1-8659) and Celma Mastery Ovarian Cancer Foundation. UCI: the UCI ovarian cancer study is supported by the National Cancer Institute, National Institutes of Health (grant R01-CA058860) and Lon V Smith Foundation (grant LVS-39420). UHN: Princess Margaret Cancer Centre Foundation – Bridge for the Cure. UKR: Cancer Research UK (C490/A6187) and UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge. WMH: National Health and Medical Research Council of Australia (Enabling Grants ID 310670 and ID 628903), Cancer Institute NSW (Grants 12/RIG/1-17 and 15/RIG/1-16), NSW Ministry of Health, AstraZeneca Pty, Medical Research Future Fund (Australia), Rivkin Center and University of Sydney. WOC: National Science Centre (N N301 5645 40) and Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw.

References

1. Koonings PP, Campbell K, Mishell DR Jr, et al. Relative frequency of primary ovarian neoplasms: a 10-year review. *Obstet Gynecol* 1989; 74:921-6.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-49.
3. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol* 2004;28: 496-504.
4. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. *Am J Surg Pathol* 2007;31:1168-74.
5. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a Gynecologic Oncology Group study. *Cancer* 2012;118:3087-94.
6. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II–IV low-grade serous carcinoma of the ovary. *Obstet Gynecol* 2006; 108:361-8.
7. Kurman RJ, Carcangiu ML, Herrington CS, et al, editors. *WHO classification of tumours of the female reproductive organs*. 4th ed, vol 6. Geneva: WHO Publications; 2014.
8. O'Neill CJ, Deavers MT, Malpica A, et al. An immunohistochemical comparison between low-grade and high-grade ovarian serous carcinomas: significantly higher expression of p53, MIB1, BCL2, HER-2/neu, and C-KIT in high-grade neoplasms. *Am J Surg Pathol* 2005;29:1034-41.
9. May T, Virtanen C, Sharma M, et al. Low malignant potential tumors with micropapillary features are molecularly similar to low-grade serous carcinoma of the ovary. *Gynecol Oncol* 2010;117:9-17.
10. May T, Shoni M, Crum CP, et al. Low-grade and high-grade serous Mullerian carcinoma: review and analysis of publicly available gene expression profiles. *Gynecol Oncol* 2013;128:488-92.
11. Hunter SM, Anglesio MS, Ryland GL, et al. Molecular profiling of low grade serous ovarian tumours identifies novel candidate driver genes. *Oncotarget* 2015;6:37663-77.
12. Etemadmoghadam D, Azar WJ, Lei Y, et al. EIF1AX and NRAS mutations co-occur and cooperate in low-grade serous ovarian carcinomas. *Cancer Res* 2017;77:4268-78.
13. Singer G, Oldt R 3rd, Cohen Y, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst* 2003;95:484-6.
14. Kurman RJ, Shih leM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. *Int J Gynecol Pathol* 2008;27:151-60.
15. Santillan A, Kim YW, Zahurak ML, et al. Differences of chemoresistance assay between invasive micropapillary/low-grade serous ovarian carcinoma and high-grade serous ovarian carcinoma. *Int J Gynecol Cancer* 2007;17:601-6.
16. Grabowski JP, Harter P, Heitz F, et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase. *Gynecol Oncol* 2016; 140:457-62.
17. Schmeler KM, Sun CC, Bodurka DC, et al. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol* 2008;108:510-4.
18. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609-15.

19. Wong KK, Lu KH, Malpica A, et al. Significantly greater expression of ER, PR, and ECAD in advanced-stage low-grade ovarian serous carcinoma as revealed by immunohistochemical analysis. *Int J Gynecol Pathol* 2007;26:404-9.
20. Fader AN, Bergstrom J, Jernigan A, et al. Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced low-grade serous ovarian carcinoma: Reducing overtreatment without compromising survival? *Gynecol Oncol* 2017;147:85-91.
21. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. *J Clin Oncol* 2017;35:1103-11.
22. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol* 2013;14:134-40.
23. Monk BJ, Grisham RN, Marth C, et al. The MILO (MEK inhibitor in low-grade serous ovarian cancer)/ENGOT-ov11 study: a multinational, randomized, open-label phase 3 study of binimetinib (MEK162) versus physician's choice chemotherapy in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum [abstract]. *J Gynecol Oncol* 2015; 33(15 suppl). doi: 10.1200/jco.2015.33.15_suppl.tps5610.
24. Huang RS, Johnatty SE, Gamazon ER, et al. Platinum sensitivity-related germline polymorphism discovered via a cell-based approach and analysis of its association with outcome in ovarian cancer patients. *Clin Cancer Res* 2011;17:5490-500.
25. Morgan RJ Jr, Armstrong DK, Alvarez RD, et al. Ovarian cancer, version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2016;14:1134-63.
26. Schlumbrecht MP, Sun CC, Wong KN, et al. Clinicodemographic factors influencing outcomes in patients with low-grade serous ovarian carcinoma. *Cancer* 2011;117:3741-9.
27. Nickles Fader A, Java J, Ueda S, et al.; Gynecologic Oncology Group (GOG). Survival in women with grade 1 serous ovarian carcinoma. *Obstet Gynecol* 2013;122:225-32.
28. Shih KK, Chi DS. Maximal cytoreductive effort in epithelial ovarian cancer surgery. *J Gynecol Oncol* 2010;21:75-80.
29. May T, Comeau R, Sun P, et al. A comparison of survival outcomes in advanced serous ovarian cancer patients treated with primary debulking surgery versus neoadjuvant chemotherapy. *Int J Gynecol Cancer* 2017;27:668-74.
30. Stewart JM, Tone AA, Jiang H, et al. The optimal time for surgery in women with serous ovarian cancer. *Can J Surg* 2016;59:223-32.
31. Horowitz NS, Maxwell GL, Miller A, et al. Predictive modeling for determination of microscopic residual disease at primary cytoreduction: an NRG Oncology/Gynecologic Oncology Group 182 study. *Gynecol Oncol* 2018;148:49-55.
32. Rosen B, Laframboise S, Ferguson S, et al. The impacts of neoadjuvant chemotherapy and of debulking surgery on survival from advanced ovarian cancer. *Gynecol Oncol* 2014;134:462-7.
33. May T, Altman A, McGee J, et al. Examining survival outcomes of 852 women with advanced ovarian cancer: a multi-institutional cohort study. *Int J Gynecol Cancer* 2018;28:925-31.
34. Gockley A, Melamed A, Bregar AJ, et al. Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstet Gynecol* 2017;129:439-47.
35. Scott SA, Fernandez ML, Kim H, et al. Low-grade serous carcinoma (LGSC): a Canadian multicenter review of practice patterns and patient outcomes. *Gynecol Oncol* 2020;157:36-45.
36. Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *J Clin Oncol* 2020;38:3753-62.