Secondary cytoreductive surgery for recurrent low-grade serous ovarian carcinoma: A systematic review and meta-analysis

Rebecca M. Goldberg a, Soyoun Rachel Kim b, Rouhi Fazelzad c, Xuan Li d, Theodore J. Brown a,e, Taymaa May b,e,*

HIGHLIGHTS
• SCS may improve survival in patients with recurrent LGSC when complete cytoreduction is achieved.
• Optimal SCS may improve survival in patients with recurrent LGSC to a lesser extent than complete SCS.
• SCS as the initial treatment at recurrence is associated with better survival compared to chemotherapy prior to surgery.
• Short platinum-free interval did not appear to be associated with worse survival in patients undergoing SCS.
• Extensive residual disease is associated with worse survival outcomes following secondary cytoreduction.

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ABSTRACT
Objectives. Low-grade serous ovarian cancer (LGSC) is a relatively chemo-resistant disease with limited effective treatment options for patients with recurrence. Secondary cytoreductive surgery (SCS) is commonly offered at recurrence, although any benefit this has on survival is not fully determined. This review evaluates the impact of SCS, including residual disease, on progression-free survival (PFS) and overall survival (OS) in recurrent LGSC.

Methods. A comprehensive search of Medline ALL, Embase Classic + Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science was conducted to obtain studies evaluating optimal or complete SCS versus suboptimal SCS and the amount of residual disease in recurrent LGSC. Meta-analysis was performed and PFS and OS outcomes were calculated.

Results. 10 of 5296 studies screened, 350 progressed to full-text review, with 9 ultimately selected for inclusion in the systematic review. Two studies met criteria for meta-analysis of PFS and of OS. The presence of visible residual disease at the conclusion of SCS negatively impacted PFS (HR = 3.51, 95% CI = 1.72–7.14), whereas SCS with no residual disease significantly improved OS (HR = 0.4, 95% CI = 0.23–0.7) in patients with recurrent LGSC. Diffuse and extensive disease distribution was inversely linked to survival. In addition, SCS as an initial treatment for recurrent LGSC was associated with superior survival in comparison to chemotherapy. A short platinum-free interval was not associated with worse survival in this cohort.

Conclusions. Complete SCS, and to a lesser extent optimal SCS, are associated with improved PFS and OS in patients with recurrent LGSC. SCS may be a better initial treatment strategy than systemic chemotherapy for recurrent disease. Patients with recurrent LGSC should be evaluated for the role of SCS based on disease distribution and functional status, irrespective of the platinum-free interval. Prospective studies are needed to further study the role of SCS in patients with recurrent LGSC.

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* Corresponding author at: Princess Margaret Cancer Center, OPG Wing, 6-811, 610 University Avenue, University Health Network, Toronto, ON M5G 2M9, Canada.
E-mail address: taymaa.may@uhn.ca (T. May).

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1. Introduction

Serous ovarian cancer is the most common subtype of epithelial ovarian cancer (EOC), and can further be subdivided into high-grade and low-grade malignancies [1]. High-grade serous ovarian cancer (HGSC) comprises 70% of EOCs, whereas low-grade serous ovarian cancer (LGSC) accounts for only 2% of EOCs and 4.7% of all serous ovarian carcinomas [2,3]. LGSC and HGSC are distinct diseases with different underlying pathogenesis, molecular events and mutational drivers [4]. In addition, the two subtypes demonstrate notable differences in clinical risk factors. In comparison to HGSC, LGSC is associated with a younger mean age at diagnosis (43 years for low-grade, 61.2 years for high-grade), a more indolent growth pattern, and prolonged PFS and OS as compared to HGSC [5–7].

Despite these differences, most patients with advanced or recurrent serous ovarian cancer are treated with similar systemic chemotherapy regimens [8]. Treatment options for recurrent ovarian malignancy typically consist of systemic chemotherapy, targeted therapies and, in some cases, secondary cytoreductive surgery (SCS) [7]. Response to chemotherapy in the recurrent setting is low in LGSC patients. Gershenson et al. evaluated 58 patients with recurrent LGSC and found an overall response rate of 4.9% and 2.1% for platinum-responsive and -resistant tumours, respectively [9]. This is particularly concerning given that more than 70% of patients with LGSC will develop recurrent disease, and underscores the crucial need for evidence-based interventions to improve the treatment of recurrent LGSC [10,11].

Few studies have addressed the role of SCS as a treatment for recurrent LGSC. Many studies investigating the role of secondary cytoreduction include patients with various subtypes of epithelial ovarian tumors, and may include few patients with LGSC [12–14]. Three recent multicenter randomized control trials (RCTs) investigated the survival benefits of SCS in recurrent ovarian cancer with conflicting results [12–14]. A limited number of patients with LGSC were enrolled in those trials. Hence, there’s a lack of clarity regarding the role and timing of SCS in the management of patients with recurrent LGSC. To date, no systematic review or meta-analysis has been conducted summarizing the relevant literature to address this question.

The objective of this systematic review and meta-analysis is to evaluate the impact of SCS and the amount of residual disease on PFS and OS in patients with recurrent LGSC.

2. Methods

This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID #CRD42021227584) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15] (Supp. Table #1).

Studies were included in the systematic review if they met the following inclusion criteria: 1. All randomized control trials, non-randomized trials, exploratory database analyses, prospective and retrospective cohort studies, and conference abstracts, 2. Includes patients with recurrent LGSC or common surrogate markers of LGSC (advanced/recurrent serous ovarian tumours of low malignant potential (LMP) [16], grade 1 serous epithelial ovarian cancer, or micropapillary serous ovarian carcinoma (MPSC)) [17], 3. Secondary, tertiary, or quaternary cytoreduction was evaluated, 4. Survival outcomes were reported for LGSC patients or survival for LGSC patients was analyzed in a univariate or multivariate model, 5. English language publication.

Studies that met the following additional criteria were selected for inclusion into meta-analyses of PFS and OS: 1. Evaluation of PFS or OS were available following SCS in patients with no residual disease as compared to patients with evidence of residual disease 2. Statistical ratios (hazard ratio (HR), odds ratio (OR), or risk ratio (RR)) for PFS or OS were separately reported for patients with residual disease at SCS, and patients with no residual disease at SCS.

Studies were excluded from the systematic review and meta-analysis if the following criteria were met: 1. Focused on second-look surgery, secondary surgery with palliative intent, interval cytoreductive surgery following neoadjuvant chemotherapy in patients with primary or recurrent disease, re-operations following primary cytoreduction in the peri-operative setting, and administration of hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of SCS. 2. Review articles and case reports.

An extensive literature search was performed in Medline ALL (Medline and Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations), Embase Classic + Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, all from the OvidSP platform; and Web of Science from Clarivate Analytics. Publication dates ranged from the inception of the databases to February 2021. Where available, both controlled vocabulary terms and text words were used. There were no language restrictions. Where applicable, the search was limited to humans and prognosis studies. The prognosis filter by HIRU was adapted with additional terms to ensure the robustness of the methodological filter for this topic (Table S1- Medline ALL search strategy) [18].

All references obtained from database searches were imported into Endnote X9 reference management software. Subsequently, all references were imported to Covidence (https://www.covidence.org/), a web-based software platform for screening and data extraction, for removal of duplicates. Using Covidence, two authors (RG and TB) independently screened the titles and abstracts of all studies to determine eligibility. Abstracts were excluded if they did not meet the inclusion criteria. Eligible abstracts automatically progressed into the full-text screen, and the full text versions of studies were downloaded into Covidence and assessed to confirm eligibility, with a consensus reached for studies with dissenting opinions. All outstanding conflicts between RG and TB were resolved by a third reviewer, TM.

Two reviewers (RG and TB) independently extracted relevant data from the eligible studies. This included publication information (first
The primary outcomes assessed were PFS and OS. Outcomes were collected for the whole study populations, and for subgroups that achieved complete SCS to no evidence of residual disease, or suboptimal SCS with evidence of residual disease. Hazard ratios were reported for factors predictive of PFS or OS in multivariate analyses.

Risk of bias was assessed in the two non-randomized studies included for meta-analysis using the Cochrane Risk of Bias in Non-Randomized Studies (ROBINS)-1 tool [19]. The remaining seven studies were assessed for bias using a modified version of the ROBINS-1 tool on the following domains: confounding bias, selection bias, information/measurement bias, sampling bias, reporting bias, detection bias and bias due to co-interventions.

Survival data from all studies were included in the qualitative synthesis and three studies were pooled for quantitative synthesis. Fixed-effect models were used for meta-analyses of PFS and OS on the studies investigating patients having complete SCS with no residual disease compared with those with suboptimal SCS with evidence of residual disease remaining at the conclusion of surgery. The combined hazard ratios and 95% confidence intervals (CI) of PFS and OS were estimated and presented in forest plots. A P-value of less than 0.05 was defined as statistically significant. Analyses were conducted using R 3.6.1.

3. Results

A total of 7662 studies were retrieved from the literature search. Following the removal of 2366 duplicates, the titles and abstracts of 5296 studies were screened. Of these, 350 studies progressed to the full-text review for eligibility assessment, with eight published studies and one conference abstract ultimately selected for inclusion in the systematic review [17,20–27]. Two of the eight studies were selected for meta-analysis of PFS [20,21] and two for OS [17,21]. The PRISMA flow-chart outlining the review methodology is illustrated in Fig. 1.

3.1. Meta analysis

Studies by Bristow et al. and Zeng et al. were meta-analyzed for OS, including a total of 71 LGSC patients in the meta-analysis [17,21]. Both studies retrospectively analyzed a cohort of LGSC patients who underwent SCS and compared survival outcomes between patients who underwent optimal cytoreduction (defined in that cohort as residual disease <10 mm, i.e. patients who had 0 mm residual and patients who had 1–9 mm residual disease) and suboptimal cytoreduction (defined as residual disease ≥10 mm). Optimal cytoreduction was achieved in 26 (37%) patients, and 45 (63%) patients had suboptimal SCS. Overall, OS was significantly higher in patients with LGSC who underwent optimal SCS as compared to patients who had suboptimal SCS with evidence of residual disease of ≥10 mm of individual tumour deposits (HR = 0.4, 95% CI = 0.23, 0.7).

Studies by Crane et al. and Zeng et al. were included in the meta-analysis for PFS and enrolled a total of 91 patients with LGSC [20,21]. Both studies retrospectively analyzed a cohort of LGSC patients who...
<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Study Design</th>
<th>Low-grade serous OC in study (n, %)</th>
<th>Patient diagnosis</th>
<th>Study Period</th>
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<th>Types of systemic therapy used</th>
<th>Median duration of follow-up (mo.)</th>
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<tbody>
<tr>
<td>Crane et al.</td>
<td>2015</td>
<td>USA</td>
<td>Single institution retrospective chart review</td>
<td>41 (100)</td>
<td>Low-grade serous OC</td>
<td>1995–2012</td>
<td>25</td>
<td>16</td>
<td>22 Platinum-based chemo, other chemo, hormonal therapy, Bevacizumab</td>
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<td>Bristow et al.</td>
<td>2002</td>
<td>USA</td>
<td>Single institution retrospective chart review</td>
<td>26 (100)</td>
<td>Micropapillary serous OC</td>
<td>No info</td>
<td>15</td>
<td>6</td>
<td>71.4 Platinum-based chemo, other chemo, Bevacizumab</td>
<td>29.5</td>
</tr>
<tr>
<td>Zeng et al.</td>
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<td>Low-grade serous OC</td>
<td>2003–2015</td>
<td>30</td>
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<td>22 Platinum-based chemo, other chemo, hormonal therapy, Bevacizumab</td>
<td>No info</td>
</tr>
<tr>
<td>Crispens et al.</td>
<td>2002</td>
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<td>Single institution retrospective chart review</td>
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<td>Low-grade serous OC and serous ovarian tumour of LMP</td>
<td>1956–1997</td>
<td>No info</td>
<td>No info</td>
<td>68 Platinum-based chemo, other chemo, external beam radiation</td>
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</tr>
<tr>
<td>Bogani et al.</td>
<td>2018</td>
<td>Italy</td>
<td>Single institution retrospective cohort study</td>
<td>4 (2)</td>
<td>Recurrent OC</td>
<td>2001–2015</td>
<td>No info</td>
<td>No info</td>
<td>82.9 No info</td>
<td>26</td>
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<tr>
<td>Yazigi et al.</td>
<td>2020</td>
<td>France</td>
<td>Multi-institution retrospective chart review</td>
<td>47 (100)</td>
<td>Low-grade serous OC</td>
<td>2000–2017</td>
<td>No info</td>
<td>No info</td>
<td>No info No info</td>
<td>No info</td>
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<tr>
<td>Rome et al.</td>
<td>2018</td>
<td>Australia</td>
<td>Retrospective chart review</td>
<td>5 (7.7)</td>
<td>Recurrent ovarian and tubal cancer</td>
<td>1980–2015</td>
<td>No info</td>
<td>No info</td>
<td>No info Radiation, chemo</td>
<td>180</td>
</tr>
<tr>
<td>Bacalbasa et al.</td>
<td>2015</td>
<td>Romania</td>
<td>Single institution retrospective chart review</td>
<td>3 (15)</td>
<td>Recurrent OC</td>
<td>2002–2014</td>
<td>No info</td>
<td>No info</td>
<td>No info Chemo</td>
<td>No info</td>
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SCS = secondary cytoreductive surgery, GRD = gross residual disease, CGR = complete gross resection, OC = ovarian cancer, LMP = low malignant potential, chemo = chemotherapy, no info = no information.
<table>
<thead>
<tr>
<th>Author</th>
<th>Median OS (mo.)</th>
<th>Median PFS (mo.)</th>
<th>Factors Predictive of OS in Multivariate Analyses</th>
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<tr>
<td></td>
<td>Whole population</td>
<td>No GRD population</td>
<td>GRD population</td>
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<tr>
<td>Crane et al.</td>
<td>64.1</td>
<td>93.6</td>
<td>45.8</td>
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<tr>
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<td>56.2</td>
<td>61.2</td>
<td>25.5</td>
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<tr>
<td>Zeng et al.</td>
<td>64</td>
<td>92.9</td>
<td>70.42</td>
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<td>Crispens et al.</td>
<td>92.4</td>
<td>No info</td>
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</tr>
<tr>
<td>Bogani et al.</td>
<td>No info</td>
<td>40.5</td>
<td>23</td>
</tr>
<tr>
<td>Yazigi et al.</td>
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<tr>
<td>Rome et al.</td>
<td>No info</td>
<td>No info</td>
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</tr>
<tr>
<td>Bacalbasa et al.</td>
<td>No info</td>
<td>55 (*from quaternary cytoreduction)</td>
<td>16 (*from quaternary cytoreduction)</td>
</tr>
<tr>
<td>Canaz et al.</td>
<td>No info</td>
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OS = overall survival, PFS = progression-free survival, GRD = gross residual disease, SCRS = secondary cytoreductive surgery, no info = no information, chemo = chemotherapy, HR = hazard ratio, RR = risk reduction.
underwent SCS, and compared survival outcomes between patients who underwent optimal SCS (defined as presence/absence of residual disease [20] or residual disease <10 mm [21]), and suboptimal SCS. Optimal SCS was achieved in 20 (22%) patients, and 71 (78%) patients were left with evidence of residual disease following SCS. SCS with no residual disease was significantly associated with prolonged PFS when compared to patients who had residual disease at the conclusion of surgery (HR = 3.51, 95% CI = 1.72, 7.14).

3.2. Systematic review

Nine studies were selected for the systematic review. Four of those studies directly assessed the benefits of SCS in patients with recurrent LGSC [17,20–22]. The other selected studies had small number of patients who underwent SCS and had variable objectives [23–27]. The complete cytoreduction rate to no evidence of residual disease was reported in six of the studies [17,20–24] and ranged from 22% to 82.9%. Study characteristics are summarized in Table 1.

Eight studies demonstrated a survival benefit following SCS in patients with recurrent LGSC when optimal secondary cytoreduction was achieved [17,20–26]. A study presented in a conference abstract format was also selected for review; however, the cytoreduction outcome was not evaluated in that cohort [27]. Importantly, the definition of optimal cytoresection varied amongst studies. This reflects the paradigm shift in ovarian cancer cytoreductive reporting over the study period, from the classic definition of optimal cytoreduction of any residual disease <20 mm or < 10 mm to the current commonly used definition of complete cytoreduction to 0 mm, optimal cytoreduction to 1–9 mm and suboptimal cytoreduction ≥10 mm of residual disease [28]. As such, Bristow et al., and Zeng et al. defined optimal cytoreduction as any residual disease <20 mm at the conclusion of surgery [17,21], whereas Bogani et al., Canaz et al., Crispens et al., and Rome et al. classified optimal cytoreduction to 0 mm residual disease [20,22–24,26]. Details of survival outcomes are provided in Table 2.

Studies conducted by Crane et al., Bristow et al., Crispens et al. and Zeng et al. demonstrated a trend towards prolonged PFS and OS in patients who had optimal SCS as compared to patients who had suboptimal SCS [17,20–22]. Crane et al. assessed the impact of SCS on PFS and OS in 41 patients with recurrent LGSC. All study participants who underwent SCS had a median PFS of 15 months, measured from the date of surgery, and an OS of 64.1 months [20]. Notably, complete SCS to 0 mm residual disease conferred a 50-month increase in PFS and an OS of 10.8 years. In a retrospective study by Bogani et al. evaluating data from 194 patients with recurrent ovarian cancer [26], the authors found that surgery following complete SCS in patients with recurrent epithelial ovarian cancer significantly reduces the risk of death (HR = 3.52, p = 0.015). Interestingly, 6 patients in that cohort did not undergo surgery and experienced a median OS of 29.9 months [17]. This is in contrast to a median OS of 25.5 months in patients who underwent suboptimal SCS [17]. Interestingly, 6 patients in that cohort did not undergo surgery and experienced a median OS of 29.9 months [17]. This suggests that complete and optimal SCS improves survival outcomes in patients with recurrent LGSC. On the other hand, suboptimal SCS confers no survival benefit in this patient population.

Similar gains in survival associated with complete SCS, and to a lesser extent optimal cytoreduction, were demonstrated in a retrospective analysis conducted by Crispens et al. on patients with progressive or recurrent serous ovarian tumours of low malignant potential (LMP) or LGSC [22]. The authors reported an inverse relation between residual disease and mortality, with a mortality rate of 10% (1/10) in patients who had complete SCS to 0 mm residual disease, a mortality rate of 14% (1/7) in patients who underwent optimal SCS with <20 mm residual disease, and a mortality rate of 60% (6/10) in patients who had suboptimal SCS with residual disease ≥20 mm [22]. Lastly, Zeng et al. found that complete SCS resulted in a median PFS of 57.4 months, from the date of initial diagnosis, and a median OS of 92.9 months, as compared to a median PFS of 14.9 months and a median OS of 70.4 months in patients who had suboptimal SCS [21]. A multivariate analysis found that the risk of death was 2.04 times (p = 0.020) greater in patients who had residual disease at the conclusion of SCS when compared to no residual disease [21].

The remaining four studies demonstrated an increase in survival following complete SCS in patients with recurrent epithelial ovarian cancer, however it was not possible to extract survival data for patients with LGSC specifically [23–26]. Canaz et al. conducted an exploratory analysis of the North-Eastern German Society of Gynecologic Oncology (NOGGO) database to compare survival outcomes of patients with recurrent low-grade and high-grade EOC from five prospective phase II/III clinical trials [23]. Their analysis included 42 patients with low-grade EOC; 25 of whom had serous histology. Twenty-one of the 42 patients with low-grade EOC underwent SCS. Multivariate analysis demonstrated improved survival in patients who underwent SCS as compared to patients who did not undergo surgery. An inverse relation between survival and residual disease was also identified. Therefore, SCS and the amount of residual disease were independent prognostic factors impacting PFS in patients recurrent low-grade EOC [23].

In a retrospective study by Bogani et al. evaluating data from 194 patients with recurrent ovarian cancer who underwent SCS, patients who had complete cytoreduction had a 17.5-month gain in OS compared to patients who underwent suboptimal cytoreduction [24]. Importantly, while survival outcomes were not stratified by grade, the authors observed increased mortality in patients with LGCs and mucinous tumors when compared to patients with HGCs. In a univariate analysis, the reported hazard ratio (HR) was 3.52 (p = 0.015), however, this was not significant in the multivariate analysis model likely due to the small number of patients in this cohort with LGSC (n = 4). Furthermore, complete cytoresection was found to significantly reduce the risk of death in a multivariate analysis for all study participants (HR = 0.25, p = 0.01) [24]. Overall, both studies demonstrate the positive prognostic value of complete SCS to no residual disease in patients with recurrent EOC [23,24].

Bacalbasa et al. retrospectively evaluated the survival outcomes following multiple cytoreductive surgeries (secondary, tertiary and quaternary cytoreduction) in 20 patients with recurrent ovarian cancer, including 3 patients with LGSC, and found similar survival outcomes when comparing optimal vs. suboptimal cytoreduction [25]. One patient with LGSC who underwent complete quaternary cytoreduction had an OS of 28 months; whereas the other two patients in this study with LGSC underwent suboptimal cytoreduction at the time of quaternary cytoreduction and experienced an average OS of 10.5 months [25]. Lastly, Rome et al. conducted a retrospective review evaluating long-term survival outcomes following radiotherapy in patients with recurrent ovarian cancer [26]. The study included 29 patients with recurrent ovarian cancer who also had SCS, and of those, 5 patients had LGSC. Considering all 29 patients who underwent surgery, the absence of macroscopic disease after surgery significantly prolonged PFS (p = 0.014) [26].

Importantly, four studies found that surgery compared to systemic therapy as the initial treatment strategy for recurrent LGSC was associated with superior survival [17,20,21,27]. In a multivariate Cox regression analysis, Crane et al. found that proceeding directly to SCS at the time of recurrence significantly prolonged PFS (HR = 0.43, p = 0.03) [20]. Notably, Bristow et al. found that treating with chemotherapy prior to surgery at the time of recurrence was associated with a trend towards worse survival, although this did not reach statistical significance (HR = 3.89, p = 0.07) [17]. Similarly, Zeng et al. showed that preoperative systemic therapy prior to SCS was not associated with improved survival [risk reduction (RR) = 3.01, p = 0.228] [21]. In a scientific abstract, Yazigi et al. retrospectively evaluated the survival outcomes of 47 patients with recurrent LGSC and found that surgery as the initial treatment following a diagnosis of recurrence was significantly associated with improved survival (HR = 0.11, p = 10–4) [27].
These results are likely a reflection of the inherent relative chemoresistance of LGSC [9].

Five studies found that extensive and/or widespread disease was associated with worse survival outcomes following SCS, although the definition of extensive disease varied slightly across all studies [20,21,24,26,27]. Multivariate analyses evaluating factors predictive of survival conducted in studies from Crane et al. and Zeng et al. found that the presence of 3 or more tumour nodules at the time of SCS was negatively associated with PFS and OS [20,21]. Furthermore, Rome et al. reported that widespread tumour dissemination, as compared to a localized unifocal recurrence, was negatively associated with PFS [26]. Bogani et al. found that the degree of carcinomatosis was inversely associated with OS [24]. Yazigi et al. reported mesenteric disease to be negatively associated with OS [27]. Although these clinical variables are not uniform, they indicate that patients with multifocal disease, especially disease that is disseminated and that may not be amenable to complete surgical resection, are less likely to gain a survival benefit from SCS for recurrent LGCS.

4. Discussion

LGSC is a rare subtype of ovarian cancer with a high rate of recurrence and few effective systemic therapies [7,11]. Secondary surgery to cytoreduce recurrent disease is commonly offered to patients with relapsed LGSC, albeit without clear consensus regarding its effect on survival. This systematic review identified nine retrospective studies evaluating the impact of cytoreductive surgery on survival in 250 patients with recurrent LGSC.

Eight of these studies identified a significant survival benefit in patients with LGSC who underwent complete SCS to no residual disease, compared to patients who underwent suboptimal SCS with evidence of residual disease at the conclusion of surgery [27]. Three studies evaluating a total of 112 patients with LGSC who underwent SCS were included in a meta-analysis. Two studies were meta-analyzed for PFS (n = 91) and OS (n = 71), respectively. Thirty-five patients (31.2%) had no residual disease following SCS, and 77 patients (68.8%) had evidence of residual disease following SCS. The presence of residual disease was inversely associated with PFS (HR = 3.51, 95% CI = 1.72–7.14). Similarly, no residual disease was significantly associated with improved OS (HR = 0.4, 95% CI = 0.23–0.7). These results are in accordance with the literature for recurrent EOC as a whole, as postoperative residual disease following cytoreduction surgery is well accepted to be an important predictor of improved survival [29,30].

Notably, patients who did not undergo SCS had worse survival when compared to patients who were treated with SCS for recurrent LGSC [17,23]. In a retrospective analysis conducted by Bristow et al., the median survival of 6 patients with recurrent MPSC/LGSC who did not undergo SCS was 31.3 months shorter than patients who underwent optimal SCS [17]. Interpretation of these results is limited by the small sample size in the non-surgery cohort and ultimately was not an independent predictor of OS in the multivariate model [17]. In another study, Canaz et al. also observed that 21 patients with low-grade ovarian malignancies who did not undergo SCS had worse PFS when compared to those treated with SCS [23]. Overall, these results suggest that SCS may confer a survival advantage to patients with LGSC with relapsed disease if complete cytoreduction, and to a lesser degree optimal cytoreduction, can be achieved.

It is imperative to acknowledge that there’s a lack of level one evidence evaluating this question and all studies included in this review harbor an element of selection bias inherent to the retrospective nature of the study design. All studies retrospectively evaluated patients who underwent surgery and thus were selected as adequate surgical candidates, which may have inflated the impact of SCS on survival. Moreover, the analysis is limited by confounding bias given the lack of stratification by systemic chemotherapies, endocrine therapies or targeted therapies. Lastly, this review included data from a recent scientific abstract, which has limited information and has not undergone a peer-review [27].

Most studies included in this review did not contain an adequate comparator group of patients with recurrent LGSC who did not receive surgery. Therefore, it is not possible to formally evaluate whether SCS is more beneficial than systemic therapy alone in patients with recurrent LGSC based on the available literature. Acknowledging this inherent limitation, we identified four studies which found that chemotherapy as an initial treatment strategy for recurrence negatively affected survival compared to proceeding directly to surgery at the diagnosis of recurrence [17,20,21,27]. These results are likely a reflection of the relatively low chemotherapy response rates characteristic of LGSC tumours [5,9,31]. These findings suggest that all patients with LGSC should be evaluated for surgical candidacy upon a diagnosis of recurrence.

Achieving optimal cytoreduction at SCS is only possible in a select group of individuals and it is well documented in the studied literature that surgery only provides a survival benefit if complete or optimal cytoreduction is achieved [29,30]. Hence, identifying patients most likely to achieve complete or optimal cytoreductive outcomes is critical to allow for proper patient selection and avoid futile surgery [24]. Various models have attempted to identify factors predictive of complete and optimal SCS including the commonly referenced Memorial Sloan Kettering (MSK) [32] and AGO-OVAR [33] models. In a 2006 retrospective analysis of patient data, the AGO OVAR committee identified three pre-operative factors predictive of complete cytoreduction in recurrent ovarian carcinoma: 1- complete resection at primary surgery, 2- good performance status, and 3- absence of ascites [33]. These criteria were subsequently validated in the DESKTOP II trial, which was the first prospective study of its kind [34]. Conversely, Chi et al. proposed the ‘MSK’ criterion for patient selection for optimal secondary cytoreduction in 2006. Those included unifocal as opposed to multifocal site of recurrence, lack of carcinomatosis, and prolonged platinum-free interval (6–12 months, 12–30 months, or > 30 months) [32].

Both models have performed fairly well when retrospectively applied [24,35]. However, some studies suggest that they may be too strict and exclude certain patients who may still benefit from SCS [36,37]. Additionally, these models have not been formally validated on patients with LGSC. Tumor grade and histology was not reported in DESKTOP I or II [33,34], and although the validation of the MSK criterion included 12 patients with well differentiated tumors, the histology of these tumors was not indicated [32]. Therefore, these models should not be strictly applied to patients with recurrent LGSC, and recurrent disease beyond these selection criteria should not be an automatic exclusion of patients from being considered for SCS. We believe that patients with disease recurrence that appears amenable to optimal resection on imaging should be considered for SCS given the retrospective data presented in this review showing significant benefit to SCS in this patient population.

More recently, the classical understanding of platinum sensitivity and the platinum-free interval as an indicator of treatment response has been deemed less relevant when deciding treatment in LGSC recurrence [38]. This is particularly pertinent since LGSC patients exhibit low response rates to platinum-based agents [9]. Although our review could not assess whether platinum sensitivity impacted survival outcomes following surgery in patients with recurrent LGSC, the survival gain associated with complete and optimal SCS seen in the reviewed studies do support the notion that patients with recurrent LGSC, many of whom were platinum-resistant, may derive benefit from secondary surgery and should not be excluded from this procedure based solely on their sensitivity to platinum-based agents. Similarly, Canaz et al. demonstrated that the platinum-free interval was not a significant prognostic factor of survival in patients with recurrent low-grade EOC [23]. Despite this data, Petriil et al. noted that patients with recurrent LGSC continue to be classified and managed based on their platinum-free interval, even though evidence indicates it is not a prognostic factor in this population.
The authors argue that in addition to the individual's platinum status, other factors such as performance status and extent of disease should be considered when evaluating candidacy for secondary cytoreduction. The results of our systematic review support this conclusion, as the presence of extensive, widespread disease was inversely associated with survival in five of the examined studies. Moreover, it is prudent to discuss the emerging evidence from three recent phase III trials evaluating the role of SCS in platinum-sensitive recurrent ovarian cancer in the context of this review. Enrollment of patients with LGSC was limited across all trials. GOG-0213 included seven patients with grade 1 serous carcinoma/LGSC and inclusion of patients with LGSC was not specified in SOC-1 or DESKTOP III. Furthermore, while survival outcomes were stratified by various epithelial histotypes, serous histology was not subdivided into low-grade and high-grade. Given the known pathological, genomic, molecular, and clinical differences between low-grade and high-grade serous cancers, it is unclear whether the results of these trials can be extrapolated to inform treatment in patients with LGSC.

Given the rarity of LGSC and the variation in clinic practice amongst treating oncologists, it may be challenging to conduct a multicenter, randomized trial evaluating the role of SCS in patients with recurrent LGSC as compared to systemic therapy. Our data suggest that chemotherapy as an initial treatment strategy for recurrent LGSC was associated with worse survival when compared to SCS, emphasizing that delaying surgery in eligible candidates may be harmful. Since the results of the reported phase III trials including GOG-0213, DESKTOP III and SOC-1, do not directly apply to patients with LGSC, treating physicians must rely on evidence from retrospective studies focused on patients with LGSC in conjunction with the above level I data to guide treatment of patients with recurrent LGSC.

In conclusion, we identified nine retrospective studies evaluating the impact of secondary cytoreductive surgery as a treatment for recurrent low-grade serous ovarian cancer. Studies demonstrated an improved PFS and OS in patients who underwent complete cytoreduction, and to a lesser extent optimal cytoreduction, as compared to suboptimal cytoreduction. The results of this meta-analysis found that PFS and OS were prolonged in patients with recurrent LGSC who undergo secondary cytoreduction with no residual disease as compared to cytoreduction with evidence residual disease at the conclusion of surgery. This synthesis cannot conclusively indicate that surgery should be offered to all patients with recurrent LGSC given the significant selection and confounding bias present in all included studies. However, our results do suggest that patients with LGSC who experience disease relapse may derive benefit from complete or optimal cytoreductive surgery and thus should be evaluated for surgical candidacy based on their functional status and disease distribution, independent of their platinum-free interval. Prospective studies in recurrent LGSC are needed to supplement and strengthen existing evidence.

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Bristow et al. 2002</td>
<td>0.05 (0.01, 0.43)</td>
</tr>
<tr>
<td>Zeng et al. 2017</td>
<td>0.49 (0.27, 0.84)</td>
</tr>
<tr>
<td>Combined effect</td>
<td>0.4 (0.23, 0.7)</td>
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**Intervention: secondary cytoreduction with no gross residual disease**

Fig. 2. Forest plot for OS. Two studies qualified for inclusion in the meta-analysis of OS. An overall positive effect was evident in patients who received the intervention (SCS with no evidence of residual disease) vs. control (SCS with residual disease). SCS = secondary cytoreductive surgery, OS = overall survival, HR = hazard ratio, CI = confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crane et al. 2015</td>
<td>3.83 (1.32, 11.19)</td>
</tr>
<tr>
<td>Zeng et al. 2017</td>
<td>3.27 (1.26, 8.47)</td>
</tr>
<tr>
<td>Combined effect</td>
<td>3.51 (1.72, 7.14)</td>
</tr>
</tbody>
</table>

**Intervention: secondary cytoreduction with no gross residual disease**

Fig. 3. Forest plot for PFS. Two studies qualified for inclusion in the meta-analysis of PFS. An overall positive effect was evident in patients who received the intervention (SCS with no evidence of residual disease) vs. control (SCS with residual disease). SCS = secondary cytoreductive surgery, PFS = progression-free survival, HR = hazard ratio, CI = confidence interval.
Author contributions

Rebecca Goldberg helped conceptualize the project, independently screened and assessed all studies, and prepared the manuscript. Dr. Theodore Brown helped conceptualize the project, independently screened and assessed all studies, and contributed to editing of the manuscript. Rouhi Fazelzad provided the search strategy and created Table S1. Xuan Li provided statistical assistance and prepared Figs. 2 and 3. Dr. Soyoun Rachel Kim and Dr. Taymaa May helped conceptualize the project, were consulted with for their clinical expertise, reviewed the data and analyses and edited the manuscript.

Declaration of Competing Interest

The authors have no conflict of interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.10.080.

References


