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Review Article

Surgical management of recurrent ovarian cancer

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HIGHLIGHTS

- Cytoreductive surgery in platinum-sensitive recurrent ovarian cancer might be feasible and effective.
- Surgical cytoreduction can be considered for selected patients with good performance status, localized disease, and long treatment-free interval.
- Ongoing randomized trials are anticipated to determine whether and on whom to perform surgery.

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ABSTRACT

Most patients with advanced-stage epithelial ovarian cancer will experience a relapse of disease despite a complete response after surgical cytoreduction and platinum-based chemotherapy. Treatment of recurrent ovarian cancer mainly comprises various combinations of systemic chemotherapy with or without targeted agents. The role of cytoreductive surgery for recurrent ovarian cancer is not well established. Although the literature on survival benefit of cytoreductive surgery for recurrent disease has expanded steadily over the past decade, most studies were retrospective, single-institution series with small numbers of patients. Given the balance between survival benefit and surgery-related morbidity during maximum cytoreductive surgical effort, it is essential to establish the optimal selection criteria for identifying appropriate candidates who will benefit from surgery without worsening quality of life. Three phase III randomized trials for this issue are currently underway. Herein, we present contemporary evidence supporting the positive role of cytoreductive surgery and offer selection criteria for optimal candidates for surgery in the treatment of recurrent ovarian cancer.

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1. Introduction

Currently, standard treatment for patients with recurrent ovarian cancer (ROC) is not well established. Until now, systemic chemotherapy has been most commonly used for the treatment of ROC, and the majority of relevant studies have focused on which regimen is the best. Most clinical trials on systemic chemotherapy alone for ROC have reported median survival times ranging from 15 to 18 months [1]. Even worse, it was reported that the median survival time for the platinum-resistant/refractory group was approximately 12 months [2]. Recently, the addition of bevacizumab to conventional chemotherapeutics seems to provide only slight survival improvement: the median overall survival (OS) of 33.6 months in platinum-sensitive disease and 22.4 months in platinum-resistant disease [3].

In 1983, Berek et al. retrospectively analyzed the data of 32 ROC patients who underwent secondary cytoreductive surgery (SCS) [4]. Although the population of the study was heterogeneous, the rate of optimal cytoreduction (defined as the largest diameter of residual tumor <1.5 cm) was 38% and the median survival times for optimally and suboptimally debulked patients were 20 months and 5 months, respectively. The introduction of concepts regarding cytoreductive surgery for ROC has received great attention, and several recent series have reported median OS of 45–61 months in patients who underwent SCS [5]. However, the therapeutic value of cytoreductive surgery in the management of ROC has been widely debated because of the technical complexity and potential morbidity associated with surgical procedures. Moreover, there is no high level of evidence as to whether surgery in the recurrent setting improves survival, or which patients are most likely to benefit from surgery. Most gynecologic oncology surgeons still decide whether to pursue a surgical treatment plan based on their own experience and results from retrospective series, almost all of which inherently suffer from selection bias.

To put an end to this debate, three phase III randomized controlled trials (DESKTOP III, Gynecologic Oncology Group [GOG] 213, and Surgery for Ovarian Cancer Recurrence [SOCceR]) are currently underway. Herein, we will look at the role of cytoreductive surgery in ROC with regard to: (1) potential survival benefit of SCS, (2) selection criteria for optimal candidates for SCS, (3) cytoreductive surgery beyond secondary cytoreduction, and (4) special issues in SCS. The aim is to offer a preliminary answer to the question of whether and on whom to perform surgery in ROC.

2. Survival benefit of secondary cytoreductive surgery

Studies on ROC include a heterogeneous group of patients. In evaluating the survival impact of SCS, it may be useful to start out by examining the relevant literature according to platinum response category to provide a more homogeneous analysis.

2.1. Secondary cytoreductive surgery in platinum-resistant recurrent ovarian cancer

Systemic chemotherapy with a non-platinum single agent regimen with or without bevacizumab is generally recommended as the treatment of choice in platinum-resistant ROC [6], which provides the best median OS of 22.4 months (95% confidence interval [CI] 16.7–26.7 months) [3]. Unfortunately, clinical trials with newer agents and best supportive care are all we can offer to platinum-resistant ROC patients who progress on 2 consecutive therapy regimens without evidence of clinical benefit. Surgery in this platinum-resistant setting is not generally accepted as a viable option for prolongation of survival because low survival times of <10 months in this group of patients cannot justify the high morbidity rate of 24% after SCS [7].

If complete resection is possible, however, surgery gains even more importance in platinum-resistant setting than in platinum-sensitive setting because a platinum-resistant tumor has very low probability of responding to systemic chemotherapy. Petrillo et al. retrospectively reviewed a total of 268 patients with isolated platinum-resistant ROC and analyzed the survival impact of SCS in 27 patients (10.1%) [8]. SCS was shown to prolong time to progression up to the 4th-line chemotherapy and post-relapse survival (PRS) compared with chemotherapy alone (32 versus 8 months; $p = 0.002$). Isolated recurrence is rare, but may be a condition in which there is possible survival benefit from SCS with acceptable surgical morbidity in a platinum-resistant setting because complete resection is achievable.

Furthermore, if isolated relapse was located in the lymph nodes or peritoneum, the survival advantage of SCS was thought to be more evident [9]. Lymph nodes (39%) and peritoneum (33%) were reportedly the most frequent sites of platinum-resistant relapse [9]. A flow cytometric analysis demonstrated that a high proportion of tumor deposits in metastatic lymph nodes were diploid with a low S-phase fraction, which might be predictably resistant to chemotherapy and radiation therapy [10]. Penetration of drugs into targeted recurrent peritoneal tumors could be impeded by postoperative fibrotic adhesions as well as lack of functional lymphatic and blood vessels [11]. Patients with platinum-resistant disease in these areas could benefit from SCS including procedures such as lymph node debulking or peritonectomy rather than chemotherapy alone.

More recently, a group of Italian investigators reported that surgery could represent a useful adjunct to chemotherapy in the management of platinum-resistant ROC patients [9]. Inclusion criteria were as follows: platinum-resistant ROC patients who had a complete response to primary cytoreductive surgery and platinum-based chemotherapy; disease-free interval < 6 months; and no concomitant neoplasia. Patients treated with ($n = 18$) or without ($n = 18$) cytoreductive surgery were compared. OS was significantly longer in the surgery group than the control group (median OS, 67 months, 95% CI 38.7–95.2 months, versus 24 months, 95% CI 8.3–39.6 months; $p = 0.035$). However, the authors failed to show significant survival difference according to number of recurrent lesions (1 versus 2 or more lesions; $p = 0.34$) in patients receiving surgery.

2.2. Secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer

SCS has been mostly advocated as an operative procedure to be performed at some time remote (disease-free interval [DFI] of >6 to 12 months) from the completion of primary therapy [12]. Clinical practice guidelines also incorporate SCS into treatment options in platinum-sensitive recurrent disease based on the results of several studies favoring SCS over chemotherapy alone in platinum-sensitive ROC [5,13–19].

2.2.1. Non-randomized observational studies: prospective design

Not long after the pioneering report of Berek et al., and following several small retrospective studies in ROC patients undergoing SCS [4,7,20], the first prospective study was conducted by Eisenkop et al. in

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Table 1
Prognostic factors of survival after secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer in the literature with a study population >100.

	Eisenkop, 2000 (n = 106) [22]	Scarabelli, 2001 (n = 149) [23]	Zang, 2004 (n = 117) [13]	Harter, 2006 (n = 267) [5]	Chi, 2006 (n = 157) [19]	Oksefjell, 2009 (n = 789) [18]	Tian, 2010 (n = 123) [40]	Sehouli, 2010a (n = 240) [41]	Zang, 2011 (n = 1100) [35]	Petrillo, 2013b (n = 220) [33]
Young age						+				
Early initial stage								+ (<FIGO IV)		
Complete primary surgery		+								
Good performance status			+							
Previous chemotherapy	−	−								
Small tumor at recurrence (criteria)	+ (<10 cm)									
Anatomic site of relapse									+	
No ascites								+		
Few recur sites			+		+				+	
Longer DFI/PFI (criteria)	+ (>36mo)	+ (>12mo)			+ (>30mo)	+ (>24mo)			+ (>23.1mo)	+
No or small residual tumor after SCS (criteria)	+ (0 cm)	+ (≤1 cm)	+ (≤1 cm)	+ (0 cm)	+ (≤0.5 cm)	+ (≤2 cm)	+ (≤1 cm)	+ (0 cm)	+ (0 cm)	+ (0 cm)
Cycle number of salvage chemotherapy			+							

DFI, disease-free interval; FIGO, the international federation of gynecology and obstetrics; PFI, progression-free interval; SCS, secondary cytoreductive surgery.
+, protective effect; −, negative effect.
[a] Platinum-resistant ROC 20% of study population.
[b] Platinum-resistant ROC 23.2% of study population.

1995 [21]. In this study of 36 platinum-sensitive ROC patients, 83% had complete resection, which depended on GOG performance status (0–2 versus 3; $p = 0.05$) and size of largest tumor deposit (<10 cm versus. >10 cm; $p = 0.03$). The median survival in patients who had no macroscopic residual disease was significantly longer than in those with macroscopic residual disease remaining after SCS (43 months versus 5 months; $p = 0.03$). It is noteworthy that salvage chemotherapy before SCS ($p = 0.02$), a preoperative GOG performance status of 3 ($p = 0.01$), and a short DFI after completion of primary treatment ($p = 0.01$) had a deleterious impact on survival. Five years later, the same study group confirmed the results of their earlier series through a larger prospective study of 106 platinum-sensitive ROC cases [22]. The complete cytoreduction rate was 82.1%. Multivariate analysis showed that survival was independently influenced by DFI, the completeness of cytoreduction, the use of salvage chemotherapy before SCS, and the largest size of recurrent tumors (Table 1).

Another prospective study was conducted by Scarabelli et al. in 2001 [23]. They reported similar results. Of three independent prognosis-associated factors, including DFI, chemotherapy before SCS, and residual tumor after SCS, residual tumor was the most strongly predictive factor of survival (hazard ratio [HR], 2.65; 95% CI 1.43–4.92). The conclusions of this study emphasized that preoperative chemotherapy affected SCS. A high proportion (81%) of study patients with DFI >24 months received extensive chemotherapy before SCS, and the OS of this population, unexpectedly, was not correlated with DFI (2-year OS, 22.3%, 62.9%, and 22.7% for DFI 7–12, 13–24, and >24 months, respectively).

2.2.2. Non-randomized observational studies: retrospective design

Since the Scarabelli study, a large number of small retrospective studies have supported the clinical benefit of SCS in platinum-sensitive ROC [24–30]. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) I trial by Harter et al. in 2006, a multi-institutional exploratory study of 267 patients based on data from a retrospective analysis of hospital records, was originally intended to develop criteria for selecting patients who might benefit from SCS in ROC [5]. The DESKTOP I trial reported that surgery in platinum-sensitive ROC could improve median OS up to 45.2 months if complete resection was achieved. They failed to show a significant survival difference between residual tumor after SCS of 0.1–1.0 cm and >1.0 cm (19.6 months versus 19.7 months; $p < 0.0001$). In a retrospective study by Oksefjell et al., the survival outcomes of 789 patients, including 217 who had SCS followed by chemotherapy and 572 who had chemotherapy alone, were compared [18]. The median OS was 4.5 years, 2.3 years, and 0.7 years in patients who underwent SCS with residual tumor 0 cm, ≤2 cm, and >2 cm, respectively ($p < 0.001$). The median OS of patients treated with chemotherapy alone was 13.2 months. There is accumulating evidence for a favorable prognosis in localized recurrence at one or two sites when successful SCS is performed [13,22,31]. Of note, the survival benefit of SCS performed in the setting of isolated lymph node recurrence has been reported to be significant [22,32]. However, even in a localized recurrence at one or two sites, the anatomic site of the relapse could also influence the survival outcome. Petrillo et al. examined a large retrospective series of ovarian cancer patients with localized relapse at a single anatomic site and <3 nodules [33]. They showed that the anatomic site of relapse was an independent prognostic factor for duration of post-relapse survival (PRS) (median PRS, 41, 63, and 24 months for relapse in the peritoneum, abdominal lymph nodes, and parenchymal organs, respectively, $p = 0.001$).

Peritoneal carcinomatosis is commonly encountered in approximately 70% of ROC [1], and is a negative predictor for complete resection, but has not been shown to be a prognostic factor if complete resection is feasible [34].

2.2.3. Non-randomized observational studies: systematic reviews or pooled analysis

In 2009, Bristow et al. published results of a meta-analysis to determine the relative effect of multiple prognostic factors on overall post-recurrence survival time in patients with ROC undergoing SCS [12]. A total of 2019 patients from 40 cohorts were included in this study. The median overall post-recurrence survival time was 30.3 months. According to the regression model estimate, the median cohort survival time ranged from 18.0 months to 48.0 months as the proportion of patients undergoing complete SCS increased from 0% to 100% (3.0-month increase in median cohort survival time/10% increase in the proportion of complete SCS). As this detailed measurement of survival benefit of SCS according to complete resection rates, there has been ongoing release of supporting evidence that the absence of residual disease after SCS is the most important prognostic factor in ROC. However, most retrospective series had fewer than 100 patients, inherently have selection bias, and were performed in a single institution, which indicated that physicians were likely to perform SCS using their own criteria for patients who were good candidates for SCS.

In order to overcome the limitations of previous reports, Zang et al. collected as many individual data as possible based on the pooled data from an international collaborative cohort [35]. They analyzed 1100 patients with platinum-sensitive ROC who underwent SCS and confirmed that complete SCS was strongly associated with improved survival (median OS, 57.7 months, 27.0 months, and 15.6 months with residual tumor zero, 0.1–1.0 cm, and >1 cm, respectively; $p < 0.0001$).

More recently, a systematic Cochrane review including nine non-randomized studies on 1194 women with ROC assessed the impact of various residual tumor sizes on OS [36]. The authors concluded that complete cytoreduction with no gross residual disease is associated with significant improvement in OS in women with platinum-sensitive ROC. Because there is no randomized controlled study demonstrating that the clinical benefit of SCS is not due to tumor biology but solely due to surgical effect, this systematic review could provide only indirect evidence supporting SCS in selected women. Therefore, using data from the Caelyx in Platinum Sensitive Ovarian patients (CALYPSO) trial, Lee et al. examined whether the OS benefit for SCS reported in observational studies is an independent effect of successful SCS on its own or simply reflects the selection of patients with good prognosis [37]. The CALYPSO trial was a phase III international, open-label, non-inferiority randomized controlled trial that compared carboplatin-pegylated liposomal doxorubicin with carboplatin-paclitaxel in patients with platinum-sensitive ROC [38]. Of the 975 patients randomized in the CALYPSO trial, 187 (18%) who underwent SCS had longer OS than the 777 (80%) who were treated with chemotherapy alone (median OS, 49.9 months versus 29.7 months; adjusted HR, 0.68; $p = 0.004$). Based on the finding of less benefit with SCS in patients with poorer prognostic features (test of trend $p < 0.001$), the authors concluded that the observed benefit of SCS in platinum-sensitive ROC might be due to selection of a subgroup of patients with good prognosis.

2.2.4. Randomized controlled studies

Currently, the best study design for minimizing selection bias and effectively controlling for confounding factors would be a prospective randomized controlled trial with SCS versus non-SCS followed by equivalent salvage chemotherapy in both groups. Although there is no level I evidence indicating that patients with platinum-sensitive ROC definitely benefit from cytoreductive surgery [39], there are three ongoing phase III randomized controlled trials (DESKTOP III, GOG 213, and SOCceR) (Table 2).

The primary outcome of the DESKTOP III study is whether maximum surgical effort in SCS followed by platinum-based combination chemotherapy can improve OS as compared to platinum-based combination chemotherapy alone in AGO-score positive patients (https://clinicaltrials.gov/) (NCT01166737). The AGO score was derived from the DESKTOP I study [5], in which multivariate analysis showed 3 factors being independently associated with complete resection: good performance status (0) according to the Eastern Cooperative Oncology Group (ECOG), macroscopically complete resection at first surgery (or alternatively, International Federation of Gynecology and Obstetrics [FIGO] stage I/II in patients with unknown residual disease after primary surgery), and absence of ascites >500 mL by radiological or ultrasound estimation [34]. Patients with all 3 factors present (AGO-score positive) are deemed to be suitable candidates for SCS, with complete resection rate of as high as 79%. The inclusion criteria of the DESKTOP III study are summarized at Table 2.

The second ongoing phase 3 randomized controlled trial, GOG 213 (NCT00565851), is a study of carboplatin and paclitaxel (or gemcitabine) alone or in combination with bevacizumab, followed by bevacizumab and SCS in platinum-sensitive, recurrent ovarian, peritoneal, and Fallopian tube cancer. For evaluation of the survival impact of the 2 treatment options, there are 2 steps of randomization: surgery or not (still open as of January 2016) and addition of bevacizumab or not (closed after August 28, 2011, when the accrual goal for evaluating the chemotherapy regimens was attained). Estimated enrollment is 1038 and the final data collection date for the primary outcome measure will be March of 2019.

The last randomized controlled trial is SOCceR; it is conducted by the Netherlands study group (www.trialregister.nl/trialreg/admin/rctview/asp?TC=3337) (NTR3337) [39]. The primary objective of the SOCceR study is to determine whether SCS followed by platinum-based chemotherapy increases progression-free survival in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or Fallopian tube cancer. The target number of enrollment is 230, and the planned closing date will be June 30, 2017. Conclusive determination of incorporation of SCS into the standard treatment of ROC should be postponed until survival outcomes of the ongoing randomized trials are reported.

3. Criteria for selecting optimal candidates for secondary cytoreductive surgery

Complete resection rates for SCS in platinum-sensitive ROC have been reported as 11% to 81% [5,13,22]. The rate of significant perioperative morbidity and mortality ranges from 0% to 88.8% and 0% to 5.5%, respectively [12]. The wide ranges of complete resection rates and perioperative morbidity/mortality suggest not only the absence of generally accepted selection criteria for identifying patients who are most likely to benefit from secondary cytoreduction but also the urgency of developing these criteria to optimize surgical treatment and avoid inadvertent delay of indicated chemotherapy.

Development of selection criteria for identifying optimal candidates for SCS should be based on prognostic factors that independently correlate with survival outcomes. Many small retrospective studies reported their own independent prognostic factors through multivariate analyses. Table 1 summarizes those prognostic factors from studies with >100 patients. The listed studies unanimously indicate that complete resection without residual tumor is one of the independent prognostic factors, and must be achieved to derive a significant survival advantage from SCS [5,13,18,19,22,23,40,41]. Criteria for complete resection vary from any visible size to 2 cm. Eisenkop et al. (median OS, 19.3 months versus 44.4 months; $p = 0.007$) and Harter et al. (median OS, 19.7 months versus 45.2 months; $p < 0.0001$) showed that any size of residual tumor significantly worsens survival [5]. In a study by Chi et al., the median survival was 56 months for patients with residual tumor ≤0.5 cm after SCS and 27 months for patients with residual tumor >0.5 cm [19]. Zang et al. (0 cm versus ≤1 cm, $p = 0.121$; ≤1 cm versus >1 cm, $p = 0.0002$; and 0 cm versus >1 cm, $p = 0.0011$) and Sehouli et al. (median OS, 42.3 months, 17.7 months, and 7.7 months for patients with complete resection, tumor residuals ≤1 cm and >1 cm, respectively; $p < 0.001$) reported that size of residual tumor after SCS >1 cm was the survival determinant [13]. Oksefjell et al. used a 2-cm cut-off for prognosis-discriminating residual tumor size

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Table 2
Details of 3 ongoing phase III randomized controlled trials of secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer.

	DESKTOP III	GOG 213[f]	SOCceR
Study group	AGO study group[a]	Gynecologic Oncology Group (GOG)[e]	Radboud University Medical Center Nijmegen
Trial registration #	NCT01166737	NCT00565851	NTR3337
Estimated accrual	408	1038	230
Primary objectives	• OS in patients with platinum-sensitive recurrent ovarian cancer with a positive AGO-score	• To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases OS • To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases OS relative to second-line paclitaxel and carboplatin alone	• Progression-free survival in selected patients with first recurrence of platinum-sensitive epithelial ovarian cancer
Inclusion criteria	• First recurrence of platinum-sensitive, invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer of any initial stage • Progression-free interval of at least 6 months after end of last platinum-containing therapy, or recurrence within 6 months or later after primary surgery if the patient has not received prior chemotherapy in patients with FIGO stage I. Non-cytostatic maintenance therapy not containing platinum will not be considered for this calculation. • A positive AGO-score[b]. Obligatory requirements for a positive AGO recurrence score in platinum--sensitive disease • Compete resection of the tumor by median laparotomy seems possible • Patients who have given their signed and written consent and their consent to data transmission and processing	• Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or fallopian tube carcinoma, which is now recurrent. • Patients enrolled after August 28, 2011 must be candidates for cytoreductive surgery and consent to have their surgical treatment determined by randomization. • Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles) • All patients must have had a treatment-free interval without clinical evidence of progressive disease of at least 6 months from completion of front-line chemotherapy (both platinum and taxane); front-line therapy may have included a biologic agent. • For more, Appendix I.	• First recurrence of platinum-sensitive, invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer of FIGO stage IC-IV (FIGO system 1988) • First-line treatment consisted of complete or optimal (≤1 cm) cytoreductive surgery and a minimum of 6 courses (neoadjuvant) platinum-taxane based chemotherapy • A clinically disease-free interval of at least 6 months after end of first-line treatment, the latter defined as the day the last chemotherapy was administered. • For more, Appendix I.
Control arm	Chemotherapy only[c]	Arm I: paclitaxel or docetaxel and carboplatin	Platinum-containing chemotherapy (at least 6 cycles)
Experimental arm	Procedure/surgery with maximum effort cytoreductive surgery	Arm II: arm I and bevacizumab Arm III: gemcitabine and carboplatin Arm IV: arm III and bevacizumab	Secondary cytoreductive surgery followed by at least 6 cycles of platinum-containing chemotherapy
Estimated primary completion date[d]	July 2016	March 2019	Jun 2017[g]

[a] Collaborators: ARCAGY/GINECO GROUP; MITO; Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Austria; GlaxoSmithKline; medac GmbH; Grupo Español de Investigación en Cáncer de Ovario; NSGO; MaNGO; Cancer Research UK; Korean Gynecologic Oncology Group; Shanghai Gynecologic Oncology Group.
[b] If all 3 criteria were fulfilled: Performance status ECOG 0, No residual tumor after primary surgery (if unknown, alternatively primary FIGO stage I/II), absence of ascites (cut off < 500 mL: radiological or ultrasound estimation).
[c] Drugs can be selected on investigators' choice.
[d] Final data collection date for primary outcome measure.
[e] Sponsored by National Cancer Institute.
[f] Outline of GOG213: patients are assigned to 1 of 4 treatment groups. Patients who are not candidates for surgical cytoreduction (i.e., those for whom complete cytoreduction in the estimation of the investigator is impossible or a medical infirmity precludes exploration and debulking) are eligible to receive chemotherapy after randomization. Patients who are eligible for surgery undergo abdominal exploration with cytoreduction, and then randomized to 1 of 4 treatment arms. (After August 28, 2011, when the accrual goal for evaluating the chemotherapy regimens was attained, only the surgical randomization remains.)
[g] Planned closing date.

after SCS (median OS, 4.5 years, 2.3 years, and 0.7 years in patients with residual tumor zero, ≤2 cm, and >2 cm, respectively; $p < 0.001$) [18].

DFI or progression-free interval (PFI) following completion of primary therapy is also addressed as an important prognostic factor in most of the series listed [14,18,19,22,23,35], in which cut-off intervals longer than 12 to 36 months were used for distinguishing the better prognosis group. There were several additional prognostic factors studied in other small series: complete clinical response to platinum primary chemotherapy, GOG or ECOG performance status, absence of ascites, size of largest tumor <10 cm, number of recurrence sites 1 or 2 versus ≥3, no salvage chemotherapy prior to SCS, ≥6 cycles of salvage chemotherapy after SCS, serum CA-125 level ≤ 35 U/mL at SCS, and platelet count $<350 \times 10^9$/L at SCS [13,19,32,38,41–43].

Other than complete resection at SCS and long DFI or PFI before SCS, there are too many prognostic factors for practical use in the decision of whether or not to perform SCS. Therefore, a prognostic model predicting survival in patients undergoing SCS was developed by Zang et al. by using pooled analysis of individual data from 1100 ROC patients [35]. This risk model was a simplified scoring system for each independent prognostic factor: PFI ≤23.1 months (score 2), ascites at recurrence (score 1), multiple recurrence sites (score 1), and residual disease after SCS (0.1 cm–1 cm, score 2; >1 cm, score 4). Thus, total scores for patients with ROC ranged from 0 to 8. With a cut-off point of 2.5 in the receiver operating characteristic curve of internal validation for the discriminative performance of this model, 418 (38.0%) low-risk patients had a significantly higher median survival after SCS than 682 high-risk patients (63.0 versus 19.1 months; HR 3.65; $p < 0.0001$). Nonetheless, there is no generally accepted guideline for selecting optimal candidates for SCS.

Another reasonable basis for selection criteria for identifying appropriate candidates for SCS is the use of factors predictive of complete resection, which must be the surgical goal of cytoreduction in ROC.

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Table 3
Predictors of complete cytoreduction for platinum-sensitive recurrent ovarian cancer in the literature with a study population >100.

	Eisenkop, 2000 (n = 106) [22]	Zang, 2004 (n = 117) [13]	Harter, 2006 (n = 267) [5]	Oksefjell, 2009 (n = 789) [18]	Harter, 2011 (n = 516) [42]	Tian, 2012 (n = 1075) [14]
Early FIGO stage			+		+	+
Residual tumor after primary surgery			+		+	+
Longer DFI/PFI						+ (>16mo)
Good performance status	+		+		+	+
Few recur sites		+		+		
Absence of ascites			+		+	+
Low serum CA125 level						+ (≤105 U/mL)
Bowel resection		+				
Small tumor at recurrence	+ (<10 cm)					
Previous chemotherapy	–					

*Platinum-resistant recurrent ovarian cancer 20%.
DFI, disease-free interval; FIGO, the international federation of gynecology and obstetrics; PFI, progression-free interval.
+, protective effect; −, negative effect.

Because residual tumor after SCS is the most consistently identified prognostic factor in the literature (Table 1), factors directly predicting complete resection are more intuitively acceptable and readily applicable in a clinical setting. Similar to prognostic factors, many studies have proposed their own set of independent predictors of complete SCS (Table 3) [5,13,14,18,22,42]. Of these, most overlap with prognostic factors, suggesting that identifying characteristics that predict complete or optimal resection could be of value in targeting the subgroup of patients most likely to benefit from SCS. Solitary or localized relapse might be the most intuitive predictor of complete resection. Zang et al. found that an optimal SCS with residual tumor ≤1 cm could be achieved in 87.9% of patients with a solitary site recurrence vs. 51.2% of patients with multifocal recurrence ($p = 0.0002$) [13]. Oksefjell et al. confirmed this finding through a multivariate analysis of 217 ROC patients who underwent SCS [18]. The results indicated that the only independent predictor of the ability of SCS to remove all visible disease was localized (1 or 2 sites) relapse versus disseminated relapse, whereas age, stage, treatment-free interval (TFI), and residual tumor after primary surgery were not. In addition to several sets of individual predictive factors from single-institution series, there is accumulating evidence for the usefulness of a predictive model consisting of several factors, rather than a single characteristic, for complete cytoreduction in patients with ROC (Table 4).

Table 4
Two models of selection criteria for secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer.*
Adapted from [45] with permission from Springer.

AGO score: if all three factors are present (AGO-score positive), complete resection is feasible in 76% of the patients.

- Complete resection at first surgery (or alternatively, FIGO I/II, if residual disease unknown)
- Absence of ascites > 500 mL
- Good performance status (ECOG 0)

International Collaborative Cohort Score (Tian model)

Score	0	0.8	1.5	1.8	2.4	3.0
• FIGO stage	I/II	III/IV				
• Residual disease at first surgery (mm)	0		>0			
• Progression-free interval	≥16				<16	
• ECOG performance status	0–1				2–3	
• CA-125 at recurrence (U/mL)	≤105			>105		
• Ascites at recurrence	Absent					Present

Low risk: sum of score ≤ 4.7, complete resection feasible in 53–83%; high risk: sum of score > 4.7, complete resection feasible in 20–42%.

One of the most robust prediction models was developed by Harter et al. using data from the AGO DESKTOP I trial in 2006 [5]. In this study, a combination of good ECOG performance status (0 versus >0), early initial FIGO stage (FIGO I/II versus FIGO III/IV) or no residual tumor after primary surgery (none versus present), and absence of ascites, so called, AGO-score positive, was shown to anticipate resectability in 79% of patients. The same study group prospectively validated the AGO-score in a multicenter study with 516 patients (DESKTOP II), and confirmed a 76% complete resection rate in the group of 129 patients who were AGO-score positive [42].

Another prediction model was developed by Tian et al. based on pooled analysis of individual data for 1075 patients with ROC undergoing SCS from 7 institutions worldwide in 2012 [14]. The observed complete resection rate in this study was 40.4% (434/1075). Six variables associated with complete resection were entered into the model: initial FIGO stage (odds ratio [OR] 1.32; 95% CI 0.97–1.80), residual disease after primary cytoreduction (OR 1.69; 95% CI 1.26–2.27), PFI (OR 2.27; 95% CI 1.71–3.01), ECOG performance status (OR 2.23; 95% CI 1.45–3.44), CA-125 (OR 1.85; 95% CI 1.41–2.44), and ascites at recurrence (OR 2.79; 95% CI 1.88–4.13). Patients were categorized as low-risk if the total risk scores were in the range of 0–4.7, which was the sum of the risk scores of the 6 predictors assigned by dividing the beta coefficient from the logistic regression model by 0.34. The low-risk group had a higher complete resection rate than the high-risk group (53.4% versus 20.1%; OR 4.55; 95% CI 3.43–6.04). This finding was confirmed by external validation using additional data on 117 patients, and sensitivity and specificity of this model were 83.3% and 57.6%, respectively.

More recently, van de Laar et al. reconfirmed the performance of the Tian prediction model and compared the performance with that of the AGO score through external validation using a Dutch population-based database with 408 patients [44]. In this study, the positive predictive values of both the AGO score and the Tian model for complete SCS were high (82.0% and 80.3%, respectively). Both models have 2 characteristics in common with the components in their own models: good performance status and absence of ascites. Good performance status and absence of ascites were also shown to be independently associated with complete resection in this external validation cohort [44]. However, the false negative rate was also high (68.5% and 55.6%, respectively). In other words, many patients were AGO-score positive or at high-risk in the Tian model, but were treated with complete SCS. In addition, neither predictive model includes imaging findings that indicate localized versus multifocal recurrence, the most intuitive predictor of complete resection [45]. The AGO score could identify suitable candidates for SCS but failed to prove an independent prognostic value, thus suggesting the success of surgery alone [44,46]. In a recent study from U.S., these findings were also observed [47]. Not only 84.3% of

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AGO-score positive cases but also 64.4% of AGO-score negative cases reached complete resection at SCS. Among those with complete SCS, AGO score was not associated with survival benefit. An ongoing phase III trial (DESKTOP III) will answer the question of whether there is any OS benefit of SCS in patients with platinum-sensitive ROC with a positive AGO-score.

More recently, an Italian study group proposed a new predictive Secondary Cytoreduction Score (SeC-S), with sensitivity and specificity of 82% and 83%, respectively [48]. The SeC-S was calculated from a logistic regression equation to determine the probability of not achieving optimal SCS using the following 4 variables: preoperative CA-125, HE4, ascites, and residual tumor at primary surgery. In this prospectively controlled study, 135 patients with ROC were assigned after a complete exploratory laparotomy with a careful visualization of the pelvis and abdominal cavity into an SCS group A or chemotherapy group B. Surgical findings used to allocate the patients into group B included: extended visceral peritoneal metastases, extensive involvement of the upper abdomen, extensive small bowel involvement, and multiple liver metastases. Using the cut-off SeC-S of 0.4375, the training set ($n = 90$, 52 from group A and 38 from group B) and validation set ($n = 45$, 25 from group A and 20 from group B) were tested for correct classification of cytoreducibility. It is noteworthy that the composition of SeC-S is quite different from that of the AGO score and Tian model. Higher specificity of the SeC-S seems to be derived from incorporation of HE4 and omitting ECOG performance status. Furthermore, SeC-S can provide the quantitative probability of non-optimal cytoreduction before SCS.

The latest proposal for selection criteria of SCS was from a Japanese study by Minaguchi et al. [49]. In 80 patients who underwent SCS, they tested combinations of 4 different favorable prognostic factors as predictors of complete resection as well as survival outcomes: TFI > 12 months, absent distant metastasis, solitary disease, and performance status 0. Complete resection rates (79%, 40%, and 33%) and OS after SCS (83 versus 67.5 months for complete/incomplete resection, respectively; 41 versus 25 months; 19 versus 19 months) correlated with the number of factors: 3–4, 2, and 0–1 (Table 5). Thus, patients with 3–4 of the 4 factors were suggested as the best candidates for SCS. Patients with 2 factors may also be considered as SCS candidates if complete resection is performed. A newly developed predictive model of complete SCS with various combinations of characteristics needs to be tested for generalizability and clinical effectiveness [56]. Chi et al. [19] proposed another guideline for selecting patients who could be offered SCS based on three factors: DFI, the number of recurrence sites, and evidence of carcinomatosis (Table 5). Both the two recommendations seem simple and easy applicable in practice although we cannot indicate which one is more effective than the other in selecting optimum candidates for SCS because of no comparison data between them.

Currently, patients who have symptomatic ascites, carcinomatosis, a short disease-free interval of <6 months after completion of primary therapy, or poor performance status, are discouraged from undergoing SCS because of the limited benefit. Diagnostic laparoscopy before SCS could be of value in accurately evaluating the abdomino-pelvic cavity and directly assessing the prospects for successful resection. Demonstration of clinical benefit of SCS itself through GOG 213 and SOCceR trials should be prioritized.

Table 5
Recommendations for secondary cytoreductive surgery based on different combinations of clinical factors.[a]
Upper combination is from [19] and lower combination is from [49] with permission from Wiley InterScience and Springer, respectively.

DFI (mo)	Single site	Multiple sites: no carcinomatosis	Carcinomatosis
6–12	Offer SCS	Consider SCS	No SCS
12–30	Offer SCS	Offer SCS	Consider SCS
>30	Offer SCS	Offer SCS	Offer SCS
No. of favorable factors[a]	Complete resection	Median OS after SCS (mo)	Treatment recommendation
3–4	Complete	83	Recommend SCS
	Incomplete	67.5	
2	Complete	41	Consider SCS, if amendable to complete resection
	Incomplete	25	
0–1	Complete	19	Chemotherapy etc.
	Incomplete	19	

SCS, secondary cytoreductive surgery.
[a] (1) TFI> 12 months, (2) absent distant metastasis, (3) solitary disease, (4) performance status 0.

4. Cytoreductive surgery beyond secondary cytoreduction: tertiary, quaternary, and more

Similar to SCS, further surgery beyond secondary cytoreduction in ROC could be beneficial based on the extrapolation of "the less the residual, the longer the survival". However, there have been only 11 retrospective studies on surgery beyond SCS (Table 6) [50–60]. All were single-institution studies except for the one by Fotopoulou et al. in 2013, which was a retrospective international multicenter study of 406 patients who underwent tertiary cytoreductive surgery (TCS) for their second recurrence [56]. The median OS of patients with no residual tumor after TCS was longer than that of patients with any residual tumor after TCS (49 months, 95% CI 42.5–56.4 months, versus 12 months, 95% CI 9.3–14.7 months; $p < 0.001$). Residual tumor in the preceding (secondary) cytoreductive surgery also showed prognostic significance in this study, which was in concordance with the 2 recently reported predictive models of complete resection, the AGO score and Tian model. Notably, tumor involvement of the middle and upper abdomen and peritoneal carcinomatosis were significant predictors of incomplete tumor resection; however, solitary upper abdominal tumor involvement without carcinomatosis appeared to have a significant protective effect against further recurrence (HR 0.47, 95% CI 0.24–0.89). This finding suggested that upper abdominal tumor involvement might not be an absolute contraindication to TCS.

Quaternary cytoreductive surgery (QCS) was first evaluated by Shih et al. at Memorial Sloan-Kettering Cancer Center in 2010 [60]. This small retrospective study of 15 ROC patients failed to show a statistically significant survival benefit of complete cytoreduction compared with that for any gross residual disease after QCS, contrary to the majority of retrospective studies on SCS. This was probably owing to the small number of patients and limited follow-up of a median of 20.8 months, in which patients with a single site of disease at QCS had longer median disease-specific survival than those with multiple sites of disease (49.9 versus 19.5 months; $p = 0.008$). It is interesting that the median TFI was only 3.7 months, suggesting a poor response to chemotherapy as shown in the high platinum-resistance rate of 47% in this cohort. More recently, the role of QCS in ROC was reevaluated in a study with a larger population of 49 patients by Fotopoulou et al. [57]. In this study, the mean OS for patients with and without residual disease was 13.4 months and 43 months, respectively ($p = 0.001$). Multifocal tumor dissemination was reported as an independent predictor of incomplete resection and lower survival. Post-QCS adjuvant chemotherapy also had a protective impact on OS. Based on these findings, they concluded that maximum surgical effort followed by chemotherapy even in the highly advanced setting of the third relapse of ovarian cancer was likely to prolong survival in a selected patient group.

The study populations are quite heterogeneous in those 11 studies in terms of patient number (15–406), platinum-sensitivity rate (42.3–100%), TFI before TCS (median 3.7–22 months), and isolated or localized recurrence (8.5–90.6%). The heterogeneity of basic patient

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Table 6
Studies on cytoreductive surgery beyond secondary cytoreduction in recurrent ovarian cancer.

	Leitao, 2004 [50]	Karam, 2007 [51]	Gultekin, 2008 [52]	Shih, 2010 (a) [53]	Fotopoulou, 2011 [54]	Hizli, 2012 [55]	Fotopoulou, 2013 (a) [56]	Tang, 2013 [58]	Shih, 2010 (b) [60]	Fotopoulou, 2013 (b) [57]	Fanfani, 2015[a] [59]
Number of patients	26	47	20	77	135	23	406	83	15	49	53
Number of cytoreduction	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Quaternary	Quaternary	Tertiary and quaternary
Study period	1990–2002	1997–2004	1992–2004	1998–2008	2000–2008	1999–2011	1997–2011	1999–2010	1991–2008	2000–2012	1997–2014
Age[b] (yr), median (range)	55.5 (30–67)	58 (28–77)	51.0 (36–68)	56.1 (27.5–74.3)	51 (22–80)	58 (43–71)	55 (16–80)	53 (29–77)	54.1 (30.7–71.4)	57 (28–76)	48 (20–69)
Platinum sensitive rate[c]	42.3%	100%	50% (PFS ≥ 18mo)	71.4%	71.9%	100%	80.3%	100%	47% (at the time of QSC)	63.3%	100%
TFI (months), median (range)	13.4 (0.5–61.3)	11 (1–66)[d]	4.0 (0 − 12)	17.0 (0.4–95)	NA	18 (8–47)	18 (2–204)	5.2 (0–82.6)[d]	3.7 (0.4–42.6)	16 (2–142)	22 (7–120)/20 (6–120)
OS (months), median (95% CI)	33.4 (20.4–46.4)[e]	24 vs. 16[e] (R0 vs. any R)	32 vs. 6 (R ≤ 2 cm vs. R > 2 cm; p = 0.9)	47.7 (25.5–69.9)[e]	19.1 (14.84–23.35)	NA	26 (19.62–32.38)	26.9	28.4 (10.7–46)[e]	10 (0.1–22)	96 (30 − 203)/135 (50–206)
Isolated recurrence[b]	42.3%	8.5% (<4)	50%	37.7%	15.6% (single IMO field)	17.4%	48.3% (no PC)	NA	53.3%	NA	90.6%/72.2%
Complete resection rate	53.8%	64%	35%	72.7%	39.3%	65.2% (R < 1 cm)	54.1%	NA	66.7%	32.6%	77.5%/66.7%
Predictor of complete resection	NA	NA	None	Single recurrence site[f]	Middle abdomen involvement; PC	None	Platinum resistance; residual disease at SCS; PC	PC; tumor sites in the middle and upper abdomen	NA	Multifocal tumor dissemination >4 IMO fields	NA
Predictor of OS	TFI > 12 months[f]; complete TCS[f]	Diffuse disease with recur site number ≥ 10	None	Complete resection[f]	Complete resection[f]; interval to primary diagnosis ≥ 3 yrs[f]; serous histology[f]	Optimal cytoreduction[f] (R < 1 cm)	[g]	PFI > 12 months[f]; mesenteric LN metastasis; TCS[f] (vs. chemotherapy)	Residual disease; number of recurrence sites (1[f] vs. multiple)	Multifocal tumor dissemination >4 IMO fields; systemic chemotherapy after QCS	NA
Perioperative morbidity	23%	26%[h]	15% (I-II)	26% (I-II, 56.6%)	31.1% (major)	13%	26% (major)	15%	46.7%[i]	28.6% (major)	NA
30-Day mortality	0	0	0	0	6%	0	3.2%	0	0	2%	NA

IMO, intraoperative mapping of ovarian cancer; NA, not available; PC, peritoneal carcinomatosis; PFS, progression-free survival; QCS, quaternary cytoreductive surgery; R, residual tumor; SCS, secondary cytoreductive surgery; TCS, tertiary cytoreductive surgery

[a] For TCS/QCS.
[b] At the time of TSC or QSC.
[c] At first adjuvant chemotherap.
[d] Progression-free interval prior to TCS.
[e] Disease-specific survival.
[f] Protective effect.
[g] Residual disease at SCS and TCS, decreasing interval to second relapse, ascites, upper abdomen involvement, nonplatinum 3rd line chemotherapy.
[h] Including 6 pulmonary embolism, 4 fistulae, and 2 myocardial infarctions.
[i] 4 grade 2, 2 grade 3, and 1 grade 4 complications.

characteristics might lead to inconsistent results between studies for complete resection rates (32.6–77.5%), perioperative morbidity (13–46.7%), and median OS (10–96 months). It is noteworthy that there were studies from the same institution among 11 studies [54,56,57]. Overlap between patients of those studies should be considered. Gultekin et al. failed to show a survival benefit associated with TCS [52]. Furthermore, there were studies reporting that none of the common clinical factors predicted an optimal TCS [52,55]. Taken together, cytoreductive surgery beyond SCS in ROC appears to lack solid evidence for its clinical usefulness. Conflicting results need to be clarified in future large-scale prospective studies.

5. Special issues in surgical cytoreduction for recurrent ovarian cancer

5.1. Quality of life

Remarkable survival benefit might be achieved with SCS in selected patients with ROC. However, the decision of whether to perform SCS in platinum-sensitive ROC or to implement chemotherapy alone depends not only on how much longer the patient survives but also on the quality of life (QoL). It is possible that potential survival gain with SCS is accompanied by a significant impairment of QoL. Nevertheless, almost no relevant series of SCS addressed QoL in patients treated with surgery plus chemotherapy or chemotherapy alone. Even the most robust data from the AGO DESKTOP II trial just included crude rates of perioperative morbidity and mortality, which cannot be compared with those of other reports, because they were described in a variety of categories without any validated assessment criteria. Mortality after SCS was also roughly reported as between 0% and 3.8% in a meta-analysis [45]. Recently, Plotti et al. published the first case-control prospective study to compare, through validated assessment tools, QoL of platinum-sensitive ROC patients treated with SCS followed by chemotherapy, versus chemotherapy alone [61]. Patients with suspected recurrence of tumor were subjected to diagnostic laparoscopy and allocated to group A ($n = 38$, surgically resectable) and group B ($n = 16$, not suitable for optimal debulking). QoL assessed by quality of life questionnaire-C30 (QLQ-C30) and The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-OV28 questionnaires were comparable between groups, except for constipation and pain, with the difference at 3 months disappearing at 6 months. Considering OS outcomes of group A versus group B at a median follow-up of 35 and 32 months, respectively (72% versus 56%; $p < 0.05$), the authors concluded that SCS plus chemotherapy seemed effective and tolerable therapeutic options in selected patients with platinum-sensitive ROC. These findings of QoL will be reappraised in phase III randomized controlled trials as one of the secondary outcome measures. Assessment tools of AGO DESKTOP III are the EORTC QLQ-30 and Functional Assessment of Cancer Therapy (FACT) NCCN Ovarian Symptom Index. The GOG 213 study measures change in QoL through FACT-Ovarian cancer (FACT-O) and the RAND-SF36. For all patients who were allocated to surgery, mixed effects of the two interventions, SCS and bevacizumab, could be reflected in QoL results. The SOCceR trial will also report QoL as one of the secondary outcome measures during the 2 years after treatment through EORTC QLQ-C30, QLQ-OV28, and EQ-5D.

5.2. Histologic type

Regarding histologic type, serous versus non-serous type was shown not to be independently associated with survival outcomes in patients with ROC [12,44]. Generally, mucinous and low-grade serous carcinomas have an indolent clinical behavior, but also have a higher degree of chemoresistance compared with high-grade serous carcinoma [62,63]. Therefore, the role of surgery may be more important in these less chemosensitive histologic types. Crane et al. reported a survival benefit of SCS for patients with no gross residual disease compared to those with gross residual disease (median OS, 93.6 versus 45.8 months; $p = 0.04$) through a single-institution, small retrospective study of 41 patients with recurrent low-grade serous carcinoma who underwent SCS [63]. However, there is only 1 study evaluating the role of SCS specifically in mucinous type ROC, even though this histologic type has fewer therapeutic options other than surgery when relapse occurs [64]. Unfortunately, this small study with 21 patients reconfirmed the very poor prognosis of mucinous ROC in which SCS, even if optimally cytoreduced, might have limited survival impact. There is urgent unmet need for large-scale research with a prospective design in this particular histology with regard to the role of SCS.

5.3. Timing of surgical cytoreduction and surveillance

The last noteworthy issue in this review is the role of SCS when recurrence including biochemical relapse is detected earlier. The Medical Research Council (MRC)/EORTC randomized trial demonstrated that early chemotherapy in asymptomatic patients based only on increased CA-125 does not prolong survival [65]. A total of 529 women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA-125 were randomized into early treatment ($n = 265$), or delayed treatment groups ($n = 264$). Treatment was started in the early group as soon as possible within 28 days of the increased CA-125 measurement, while treatment in the delayed group was not started until clinical or symptomatic relapse. Treatments in both groups according to standard local practice did not include SCS, but only used various platinum combinations. Earliest detection of recurrence—even biochemical evidence with positron emission tomography-computed tomography (PET/CT) or other biomarkers—could be useful for increasing the success rate of SCS considering that isolated or localized disease might be an important predictive factor of complete cytoreduction and improved survival [66]. Tanner et al. showed that detection of asymptomatic recurrences by routine surveillance testing was associated with a high likelihood of optimal SCS in operative candidates, and extended OS in platinum-sensitive ROC although it remained to be prospectively explored [25,67]. Fleming et al. reported that each week of delay after the first CA-125 elevation correlated with a 3% increased chance of suboptimal resection at SCS [68]. While some patients may benefit from early detection of recurrent disease and may be candidates for SCS, others may choose to delay therapy until they develop symptoms of disease recurrence. The results of the MRC/EORTC randomized clinical trial suggest that withholding treatment in the event of isolated rising CA-125 levels will not negatively affect the OS, highlighting the need for improved salvage therapies for ROC including SCS [69].

6. Conclusion

There remains an urgent unmet need for effective therapy following disease recurrence after primary treatment of ovarian cancer. SCS is gaining increasing acceptance as a viable treatment option for selected patients with platinum-sensitive ROC. A survey among Dutch gynecologists and medical oncologists on the role of surgery in the management of patients with platinum-sensitive ROC showed that most were convinced of the benefit of SCS and anticipated a better understanding of the selection criteria for optimum candidates for SCS after the release of results of 3 ongoing phase III randomized controlled trials: DESKTOP III, GOG 213, and SOCceR [70]. Until such data are available, physicians have to individualize the treatment of ROC by considering functional performance status, prior TFI and toxicity, distribution and extent of disease, and the patient's overall life goals. Currently, the strongest predictor of OS in patients with ROC who undergo SCS is maximal cytoreduction with minimal residual disease, at best, no residual disease. Complete resection should become the ultimate goal of SCS. However, there is no consensus on how much survival gain can justify operative morbidity and mortality. In order to

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exquisitely balance between the two, maximal survival gain and minimal operative morbidity and mortality, highly specialized teams and centers for this complex surgery are needed. Cost-effectiveness analysis of SCS should be considered in the decision of whether or not to perform surgery for ROC.

Conflict of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2016.04.537.

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