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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