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Overview

When should Surgery be used for Recurrent Ovarian Carcinoma?

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Abstract

Cytoreductive surgery is an important column in the treatment of primary ovarian cancer. Surgical outcome is one of the most important prognostic factors and one of the few prognostic variables that can be influenced by therapists. Retrospective studies suggested that only complete cytoreduction was associated with a benefit. Therefore, definition of predictors of complete resection is of the utmost importance to avoid surgical burden in patients with both limited benefit of the procedure and limited overall life expectancy. Two prospective multicentre randomised surgical trials in platinum-sensitive recurrent ovarian cancer (DESKTOP III [NCT #01166737] and GOG 213 [NSC #704865]) comparing secondary cytoreductive surgery followed by platinum-based chemotherapy versus chemotherapy alone have been conducted. The results of the DESKTOP III were recently presented at the American Society of Clinical Oncology meeting in Chicago. It showed a benefit of secondary cytoreductive surgery exclusively in patients with complete resection with a progression-free survival of 5.6 months ($P < 0.001$). This overview aims to support this task and concentrates on the currently available data regarding surgery in recurrent ovarian cancer.

Key words: Ovarian cancer; recurrence; secondary cytoreductive surgery

Statement of Search Strategies

The principal literature search utilized MEDLINE and Cochrane databases to identify contributions related to the topic published between January 1980 and June 2017. Key words included “ovarian cancer”, “recurrence”, “secondary cytoreductive surgery” and their combinations. Reference lists of all eligible articles were checked for other relevant studies. Conference proceedings were included. Expert contributions came from the authors.

Introduction

Most ovarian cancer patients are diagnosed with advanced disease stage [1]. Primary treatment of epithelial ovarian cancer is based on surgery and platinum-based chemotherapy with or without maintenance therapy with bevacizumab or newer targeted therapies. Macroscopically complete resection during upfront surgery is associated with the largest survival benefit, while surgery ending with large tumour bulks of 1 cm diameter or more does not alter the prognosis significantly [2]. Similar observations have been reported for recurrent ovarian cancer. Therefore, defining predictors of complete resection in recurrent disease is an urgent need for both: on the one hand selection of the right patients for surgery and on the other to prevent surgical morbidity and mortality in patients with no or only limited benefit of surgery. Systemic treatment in recurrent disease with a platinum-free interval >6 months is based on platinum chemotherapy combined with either pegylated liposomal doxorubicin [3], paclitaxel [4] or gemcitabine [5]. Additional treatment with bevacizumab to combination chemotherapy like carboplatin/gemcitabine [6] or carboplatin/paclitaxel [7] showed a significant advantage in progression-free survival (PFS), but not in overall survival. Olaparib maintenance therapy, a poly (ADP-ribose) polymerase inhibitor (PARP inhibitor), is another treatment option in patients with a BRCA1/2 mutation, a high-grade serous histology and a response to the last platinum-based chemotherapy [8]. Another study evaluating Niraparib as maintenance therapy has shown that activity of PARP inhibitors is not limited to patients with a BRCA mutation [9].

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Patients with recurrent disease and a platinum-free interval <6 months are treated with a monochemotherapy, e.g. pegylated liposomal doxorubicin [10], topotecan [11], paclitaxel weekly or gemcitabine [12]. For treatment with pegylated liposomal doxorubicin, topotecan, and paclitaxel weekly a combination with bevacizumab is possible [13].

Overview

In this review, we focus on secondary cytoreductive surgery, defined as surgery in patients with recurrent ovarian cancer after complete primary treatment, which includes primary surgery with or without chemotherapy, and a disease-free interval. The benefits of surgery, e.g. to reach a prolongation of PFS and overall survival as well as a symptom relief, need to be weighed against the risks and disadvantages, such as morbidity and mortality, hospitalisation and costs.

Surgery for platinum-resistant disease, mostly patients with residual disease after primary surgery, progressive disease during or shortly after primary chemotherapy, is usually not recommended. Morris *et al.* [14] showed a median overall survival of 9.4 months in patients with residual disease <2 cm, Segna *et al.* [15] reported a median overall survival of 8.8 months. Although surgery in this subgroup is technically feasible, its value is limited and it is accompanied by high morbidity. Salvage palliative surgery is accompanied by high mortality and morbidity rates, 10% and 51%, respectively. Salvage surgery in bowel symptoms resulting in short bowel syndrome should only be carried out in specialised centres and conservative management should be favoured as long as there is no emergency, such as bowel perforation or acute abdomen [16].

The Second Ovarian Cancer Consensus Conference described factors for the identification of suitable patients for surgery in recurrent disease: progression-free interval >12 months, response to first-line chemotherapy, feasible complete resection, good performance status and young age [17]. Also, the CA125 elevation was found to be a predictive factor for complete resection in univariate analysis [18]. In retrospective data, other predictors of beneficial surgical outcome with complete resection were the absence of preoperative salvage chemotherapy, good performance status and size of recurrent disease less than 10 cm. A recent review showed that the number of disease sites (solitary versus multiple) is an independent factor for complete resection and absence of ascites and absence of residual tumour after primary surgery were predictors for complete resection [19]. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) developed the Descriptive Evaluation of perioperative Selection KriTeria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) series. The DESKTOP I trial, a retrospective multicentre analysis, was undertaken to form a hypothesis for a panel of criteria selecting patients who might benefit from surgery in relapsed ovarian cancer and to create a predictive score for resectability, allowing patient selection for further studies [20]. Complete resection was associated with significantly longer overall survival compared with the subgroup with any residual tumour after secondary cytoreductive surgery (median 45.2 months versus 19.7 months; $P < 0.0001$) (Figure 1). Predictive parameters of complete resection were a good performance status (Eastern Cooperative Oncology Group 0), no residual tumour after primary surgery or early International Federation of Gynecology and Obstetrics (FIGO) stage at primary diagnosis (FIGO I/II) and absence of ascites in preoperative imaging (cut-off 500 ml).

The localisation of recurrent disease and therapy-free interval did not show any impact for complete resection in multivariate analysis. Peritoneal carcinomatosis was not a prognostic factor, but a negative predictor of successful surgery. In the case of complete resection of peritoneal carcinomatosis, there was no difference in overall survival

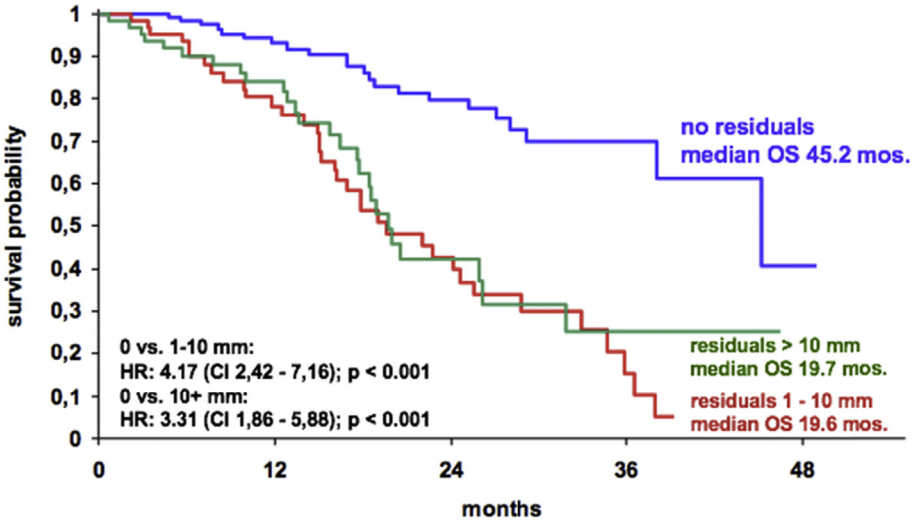

Fig 1. Overall survival of patients with secondary cytoreductive surgery with no residual tumour, residual tumour 1–10 mm and residual tumour >10 mm.

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