Abstract

Advanced ovarian cancer has a poor prognosis. Debulking surgery and platin-based chemotherapy are the cornerstones of the treatment. Primary debulking surgery has been the standard of care in advanced ovarian cancer. Recently a new strategy with neoadjuvant chemotherapy followed by interval debulking surgery has been developed. In a recently published randomized trial of the EORTC-NCIC (European Organisation for Research and Treatment of Cancer – National Cancer Institute Canada) in patients with extensive stage IIIc and IV ovarian cancer it was shown that the survival was similar for patients randomised to neoadjuvant chemotherapy followed by interval debulking compared to primary debulking surgery, followed by chemotherapy. The post-operative complications and mortality rates were lower after interval debulking than after primary debulking surgery. The most important independent prognostic factor for overall survival was no residual tumor after primary or interval debulking surgery. In some patients obtaining the goal of no residual tumor at interval debulking is difficult due to chemotherapy induced fibrosis. On the other hand the patients randomized had very extensive stage IIIc and IV ovarian cancer it was shown that the survival was similar for patients randomised to neoadjuvant chemotherapy followed by interval debulking compared to primary debulking surgery, followed by chemotherapy. The post-operative complications and mortality rates were lower after interval debulking than after primary debulking surgery. The most important independent prognostic factor for overall survival was no residual tumor after primary or interval debulking surgery. In some patients obtaining the goal of no residual tumor at interval debulking is difficult due to chemotherapy induced fibrosis. On the other hand the patients randomized had very extensive stage IIIc and IV ovarian cancer it was shown that the survival was similar for patients randomised to neoadjuvant chemotherapy followed by interval debulking surgery. Hence, selection of the correct patients obtaining the goal of no residual tumor at interval debulking is difficult due to chemotherapy induced fibrosis. On the other hand the patients randomized had very extensive stage IIIc and IV ovarian cancer it was shown that the survival was similar for patients randomised to neoadjuvant chemotherapy followed by interval debulking surgery is important. Beside imaging with CT, diffusion MRI and/or PET-CT also laparoscopy can play an important role in the selection of patients.

Introduction

Debulking surgery and platin-based chemotherapy are the cornerstones of the treatment of ovarian cancer (1). In most patients with ovarian carcinoma, the disease is diagnosed at an advanced stage and they usually have a very poor prognosis (2). Primary cytoreductive surgery (or debulking surgery) is an operation to remove as much of the tumor, and its metastases, as possible before subsequent chemotherapy is administered. Interval cytoreductive surgery (or interval debulking surgery) on the other hand is an operation performed in patients after a short course of neoadjuvant chemotherapy, usually three cycles of chemotherapy (3).
followed by interval debulking surgery, is essentially the same as for patients treated with primary debulking surgery (10) followed by chemotherapy. In contrast to the conclusions that were drawn from individual retrospective studies, the authors of a meta-analysis concluded that neoadjuvant chemotherapy is associated with a worse prognosis when compared to primary debulking surgery (11). A more recent meta-analysis of 21 non-randomized trials concluded that survival was similar in patients treated with neoadjuvant chemotherapy followed by interval debulking surgery compared to primary debulking followed by chemotherapy (12).

Recently the first trial randomizing patients with stage IIc and IV epithelial ovarian-, fallopian tube or primary peritoneal carcinoma between primary debulking surgery followed by platinum-based chemotherapy versus neoadjuvant platinum-based chemotherapy followed by interval debulking was reported by the EORTC-GCG (European Organisation for Research and Treatment of Cancer - Gynaecological Cancer Group) and NCIC Clinical Trials Group (13). In this study 718 patients were enrolled. All patients had Stage IIc or IV ovarian cancer and most of them had very extensive disease (61% metastases > 10 cm at primary debulking). The largest residual tumour was ≤1 cm after primary and interval debulking surgery in 42% and 80%, respectively. Postoperative infections, venous complications, fistula, hemorrhage and postoperative mortality tended to be higher after primary debulking surgery. The overall and progression-free survival was similar in both groups. Complete resection of all macroscopic tumor (at primary or interval surgery) was the strongest independent variable predicting overall survival. A noteworthy drop in the overall survival was noted during the first 3 months after randomization in patients undergoing primary debulking, due to postoperative mortality and to delay of the postoperative chemotherapy. In a subgroup analysis none of the following factors was associated with a better survival with one of the treatment arms: age, FIGO-stage, the presence of pleural fluid, WHO performance status, histological type, and residual tumor.

Leaving no residual tumor following primary debulking surgery was shown to be the single most important independent prognostic factor in advanced ovarian carcinoma in the EORTC-NCIC studies and in earlier retrospective studies. (10,13-19). Hence no residual tumor is currently to be regarded as the only correct definition of “optimal debulking surgery”.

One of the important questions is how to select patients for primary debulking or interval debulking surgery with the aim of leaving no residual tumor at the time of surgery. First, it should be underscored that the available randomized data are restricted to patients with Stage IIc or IV disease. Hence, primary debulking followed by chemotherapy remains the standard of care for Stage IIb and lower. Secondly, all patients should be evaluated by a gynecologic oncologist prior to deciding on primary debulking or neoadjuvant chemotherapy. However, the problem in evaluating these patients is that no predictive factors favoring one of the arms were observed in the EORTC study, except for a marginally better survival in patients randomized to primary debulking with metastases smaller than 5 cm. Surgical consultation and careful analysis of important predictive factors of debulking surgery resulting in no residual macroscopic tumor, such as co-morbidities, age, disease burden, location of metastatic sites, performance status and stage, should be taken into account when deciding whether a patient is a candidate for primary debulking surgery or for neoadjuvant therapy.

In conclusion, neoadjuvant chemotherapy followed by interval debulking surgery in stage IIc-IV ovarian, fallopian tube and peritoneal ovarian carcinoma, as included in the EORTC-NCIC study, produced similar overall and progression-free survival as primary debulking surgery followed by chemotherapy. Optimal debulking surgery with complete resection of all macroscopic lesions was the strongest independent prognostic factor for overall survival. In some patients obtaining the goal of no residual tumor at interval debulking is difficult due to chemotherapy induced fibrosis. On the other hand the patients randomized had very extensive stage IIc and IV disease and in patients with metastases smaller than 5 cm the survival tended to be better after primary debulking surgery. Hence, selection of the correct patients with stage IIc or IV ovarian cancer for primary debulking or neoadjuvant chemotherapy followed by interval debulking surgery is important. At the University Hospitals of Leuven we are using the criteria for selection as outlined in Table 1. Using these criteria, about 50–60% of the patients with stage IIc or IV disease are selected for neoadjuvant chemotherapy.

Table 1. Leuven criteria for neoadjuvant chemotherapy followed by interval debulking surgery in stage IIc and IV ovarian carcinoma (about 50-60 % of the patients with stage IIc and IV disease).

1. Tumors larger than 2 cm around the superior mesenteric artery or behind the porta hepatitis, or,
2. Intrahepatic (multiple) metastases or extraabdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes) larger than 2 cm, or,
3. Poor general condition (e.g. >80 years) making a “maximal surgical effort” to no residual tumor impossible, or,
4. Extensive serosal invasion (e.g. plaques) of the intestines necessitating bowel resections of >1.5 m.
5. Patients that cannot be (easily) debulked to no residual tumor (e.g. more than 1 bowel resection, expected operative time more than 4 hours, poor general condition, …)

Leuven criteria for neoadjuvant chemotherapy followed by interval debulking surgery in stage IIc and IV ovarian carcinoma (about 50-60 % of the patients with stage IIc and IV disease).
References


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