Primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer

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Abstract

Advanced ovarian cancer has a poor prognosis. Debulking surgery and platinum-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 randomised 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 tumour after primary or interval debulking surgery. In some patients obtaining the goal of no residual tumour at interval debulking is difficult due to chemotherapy-induced fibrosis. On the other hand the patients randomised had very extensive stage IIIc 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 IIIc or IV ovarian cancer for primary debulking or neoadjuvant chemotherapy followed by interval debulking surgery is important. Besides imaging with CT, diffusion MRI and/or PET-CT, also laparoscopy can play an important role in the selection of patients.

It should be emphasised that the group of patients included in this study had *extensive* stage IIIc or IV disease. Surgical skills, especially in the upper abdomen, remain pivotal in the treatment of advanced ovarian cancer. However, very aggressive surgery should be tailored according to the general condition and extent of the disease of the patients. Otherwise, this type of aggressive surgery will result in unnecessary postoperative morbidity and mortality without improving survival. Hence, neoadjuvant chemotherapy should not be an easy way out, but is in some patients with stage IIIc or IV ovarian cancer a better alternative treatment option than primary debulking. According to the current treatment algorithm at the University Hospitals Leuven about 50% of the patients with stage IIIc or IV ovarian cancer are selected for neoadjuvant chemotherapy.

Introduction

Debulking surgery and platinum-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 (or debulking) surgery is an operation to remove as much of the tumour, 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].

The importance of primary cytoreductive surgery in the treatment of advanced ovarian cancer of FIGO

(International Federation of Gynaecology and Obstetrics) stage III and IV was already suggested as early as 1934 [4] but it wasn't until the 1970s that Aure and colleagues [5] and Griffiths and colleagues [1] showed that the amount of residual tumour following primary surgery was an important prognostic factor in the treatment of advanced ovarian cancer. However, no prospective, randomised controlled trials are available that prove that primary debulking surgery will improve the prognosis of patients with ovarian cancer.

Role of primary- and interval debulking surgery

In the 1980s, the European Organisation for Research and Treatment of Cancer – Gynaecological Cancer Group (EORTC-GCG) launched a randomised study to investigate the role of interval debulking surgery in women who did not or could not have a successful primary debulking operation (reduction of disease to $\leqslant$1 cm). In this trial interval debulking surgery significantly lengthened survival [6]. In a later, similar study performed by the Gynecologic Oncology Group (GOG) it was revealed that the addition of interval debulking surgery to post-operative chemotherapy did not improve survival [7]. From both studies it has been concluded that, based on the EORTC trial, interval debulking surgery by an experienced gynaecological oncologist led to improvement in some patients who had not had initial optimal debulking surgery (poor medical condition, inexperienced surgeon, ...) [8]. On the other hand, based on the GOG-trial, it was concluded that interval debulking surgery did not seem to offer an advantage to patients whose primary surgery included maximal surgical effort to remove disease by a gynaecological oncologist.

Neoadjuvant chemotherapy followed by interval debulking surgery

Alternatively to primary debulking surgery, neoadjuvant chemotherapy can be administered before attempting cytoreductive surgery. This approach has been advocated by some authors, especially for the treatment of stage IV ovarian cancer or for patients with a very high metastatic tumour load (e.g. more than 1 kg), or in patients with a poor general condition. From these studies it appears that the outcome of these women, treated with neoadjuvant chemotherapy followed by interval debulking surgery, is essentially the same as for patients treated with primary debulking surgery [9] followed by chemotherapy. In contrast to the conclusions that were drawn from individual retrospective studies, the Bristow and Chi in a meta-analysis concluded that neoadjuvant chemotherapy is associated with a worse prognosis when compared to primary debulking surgery [10]. However, a more recent meta-analysis of 21 non-randomised trials concluded that survival was similar in patients treated with neoadjuvant chemotherapy followed by interval debulking surgery compared to primary debulking followed by chemotherapy, and criticised the meta-analysis of Bristow and Chi because patients treated with more neoadjuvant chemotherapy presented more often with stage IV disease and received less paclitaxel [11].

Recently the first trial randomising patients with stage IIIc 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 and NCIC Clinical Trials Group [12]. In this study 718 patients were enrolled. All patients had stage IIIc or IV ovarian cancer and most of them had very extensive disease (61% metastases $>$10 cm at primary debulking). The largest residual tumour was $\leqslant$1 cm after primary and interval debulking surgery in 42% and 80%, respectively. Postoperative infections, venous complications, fistula, haemorrhage and postoperative mortality tended to be higher after primary debulking surgery. The overall and progression-free survival was similar in both groups. Complete resection of all macroscopic tumour (at primary or interval surgery) was the strongest independent variable predicting overall survival. A noteworthy drop in the overall survival was noted during the first 3 months after randomisation in patients undergoing primary debulking. In a subgroup analysis with overall survival as endpoint, none of the following factors was associated with treatment arm: age, FIGO stage, the presence of pleural fluid, WHO performance status, histological type, and residual tumour. The debulking rates differed substantially from country to country; however, country was not a prognostic factor for overall survival. Also in Belgium, with a primary debulking rate to no residual tumour of 63% ($<$1 cm of 71%), there was no advantage of primary surgery compared with neoadjuvant chemotherapy.

Complete resection of all macroscopic disease at primary debulking surgery has been shown to be the single most important independent prognostic factor in advanced ovarian carcinoma [9,13–17], and this was confirmed for interval debulking surgery after neoadjuvant chemotherapy in our randomised

study [12]. Based on these findings there is a growing consensus that optimal cytoreduction should no longer be defined as residual tumour <1 or <0.5 cm, but as a resection without macroscopic residual tumour. Based on our results the real question is, however, what the best timing is to perform this radical operation in the individual patient with stage IIIc or IV disease, primarily or after neoadjuvant chemotherapy.

How to select patients for primary debulking or interval debulking surgery?

One important question is how to select patients for primary debulking or interval debulking surgery with the aim of leaving no residual tumour at the time of surgery. First, it should be underscored that the available randomised data are restricted to patients with stage IIIc or IV disease. Hence, primary debulking followed by chemotherapy remains the standard of care for stage IIIb and lower. Secondly, all patients should be evaluated by a gynaecologic oncologist prior to deciding on primary debulking or neoadjuvant chemotherapy. However, the problem in evaluating these patients is that no predictive factors favouring one of the arms were observed in the EORTC study, except for a marginally better survival in patients randomised 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 tumour, 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.

However, many studies have shown that it is very difficult to predict optimal debulking surgery. Laparoscopy to judge operability was used in a minority of patients. However, in addition to computed axial tomography, diffusion MRI and/or positron emission tomography [18], a diagnostic laparoscopy can provide important additional information [19–23].

Criticisms on the EORTC-GCG/NCIC Clinical Trials Group randomised trial [12]

Some authors have criticised the EORTC-GCG/NCIC Clinical Trials Groups study because in their opinion the debulking rates were too low. It should, however, be emphasised that the group of patients included in this study had *extensive* stage IIIc or IV disease. Indeed, to be eligible most patients already on imaging had obvious stage IIIc or IV disease and 61% presented at the time of primary debulking surgery (PDS) with metastases larger than 10 cm (74% larger than 5 cm). The low rate of optimal debulking in the PDS arm reflects a possible selection bias by the investigators recruiting mainly patients with very advanced stage IIIc or IV disease. The inclusion of very advanced stage IIIc and IV disease may be one of the reasons for the lower median progression-free and overall survival rates compared with some single-institution series [9,13–16].

However, it is clearly more valid to compare the results of a randomised trial to other multicentre studies or population studies. When comparing the survival results of our control group (median overall and progression-free survival in the intention-to-treat analysis of the primary debulking arm of 29 and 12 months, respectively, and 5-year survival rate of 23%) with other prospective randomised studies, we want to underscore that our study is the only prospective study excluding stage IIIa and stage IIIb disease. In addition, patients with stage IIIc disease based on para-aortic or pelvic lymph node metastases were not eligible for the current study (if smaller than 2 cm for para-aortic lymph nodes). This group of patients has a better prognosis than stage IIIc patients with intraperitoneal disease [24]. In addition, it can be expected that patients with "small" intraperitoneal stage IIIc disease were underrepresented in our study as the diagnosis of stage IIIc or IV disease had to be made prior to randomisation, and the diagnosis in these patients is often only made at the time of surgery. When taking these prognostic factors into account the survival rates are similar to the survival rates obtained in Gynecologic Oncology Group (GOG) 111 study [25], GOG (GOG132) [26], another European–Canadian study [27], and a European–Australian trial [28]. In GOG158 [29] and GOG 172 [30] only patients with stage III and less than 1 cm largest residual tumour were included.

When looking at the survival rates in population-based studies the survival rates are quite similar to the EORTC-GCG/NCIC Clinical Trials Group study [31–34].

Acceptance of neoadjuvant chemotherapy worldwide

An interesting questionnaire on neoadjuvant chemotherapy in advanced ovarian cancer was recently reported [35]. The questionnaire was sent to 1,137 members of the Unites States based Society of Gynecologic Oncology and was answered by 339 of them.

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

1. Tumours larger than 2 cm around the superior mesenteric artery or behind the porta hepatis, 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 tumour impossible, or
4. Extensive serosal invasion (e.g. plaques) of the intestines necessitating bowel resections of >1.5 m.
5. Patients who cannot be (easily) debulked to no residual tumour (e.g. more than 1 bowel resection, expected operative time more than 4 hours, poor general condition, ...)

Surprisingly, 60% of the respondents use neoadjuvant chemotherapy in less than 10% of their patients with advanced stage ovarian cancer. Of the respondents, 82% did not consider available evidence sufficient to justify neoadjuvant chemotherapy followed by interval debulking. Almost 40% of the respondents stated that more than 80% of their patients were optimally (largest residual tumour <1 cm) cytoreduced, and another 42% stated that 61–80% of their patients were optimally cytoreduced. These optimal debulking rates are excellent, but are based on statements of the respondents and not on actual patient data. In addition, the response rate to the questionnaire was only 30%, making it possible that the respondents might have a different opinion compared with the 70% non-respondents. The situation seems to be completely different in Europe. A similar questionnaire was sent to 1,177 members of the European Society of Gynaecological Oncology. Of 469 (40%) responding members, 70.2% believed there was sufficient evidence to use neoadjuvant chemotherapy followed by interval debulking for the treatment of stage IIIc and IV ovarian cancer (personal communication, I. Vergote).

Conclusions

Neoadjuvant chemotherapy followed by interval debulking surgery in stage IIIc–IV ovarian, fallopian-tube and peritoneal ovarian carcinoma, as included in the EORTC-GCG/NCIC Clinical Trials Group study, produced similar overall and progression-free survival as primary debulking surgery followed by chemotherapy, with less complications and a lower postoperative mortality. It should be underscored that the available randomised data are restricted to patients with stage IIIc or IV disease. Hence, primary debulking followed by chemotherapy remains the standard of care for stage IIIb and lower.

In some patients, obtaining the goal of no residual tumour at interval debulking is difficult due to chemotherapy-induced fibrosis. On the other hand the patients randomised in the EORTC-GCG–NCIC Clinical Trials Group study had very extensive stage IIIc and IV disease. Furthermore in patients with metastases smaller than 5 cm the survival tended to be better after primary debulking surgery. Hence, all patients should be evaluated by a gynaecologic oncologist prior to deciding on primary debulking or neoadjuvant chemotherapy. At the University Hospitals of Leuven we are using the criteria for selection as outlined in Table 1. Using these criteria, about 50% of the patients with stage IIIc or IV disease are selected for neoadjuvant chemotherapy.

Surgical skills, especially in the upper abdomen, remain pivotal in the treatment of advanced ovarian cancer. However, very aggressive surgery should be tailored according to the general condition and extent of the disease of the patients. Otherwise, this type of aggressive surgery will result in unnecessary postoperative morbidity and mortality without improving survival. Hence, neoadjuvant chemotherapy should not be an easy way out, but is in some patients with stage IIIc or IV ovarian cancer a better alternative treatment option than primary debulking.

Conflict of interest statement

The authors have no potential conflict of interest to disclose.

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