Ovarial cancer: best timing and applications of debulking surgery

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Ovarian Cancer is the fifth leading cause of death in women in the United States and the most common cause of death in women with gynaecological malignancies in most Western countries. Despite the significant advances in surgery, chemotherapy and radiotherapy, the resulting overall 5-year survival is about 40–50% [1]. In addition, millions of women remain fearful and concerned about being diagnosed with this too often fatal disease. While early detection improves the chances that ovarian cancer can be treated successfully, early cancers of the ovaries rarely cause symptoms that women would notice, or the symptoms are mistaken for menopausal ailments or intestinal illness. As a result, almost 75% of women with ovarian cancer are not diagnosed until the disease is advanced in stage with only 15–20% chances of reaching 5-year survival. Investigative efforts for the new millennium involve the areas of basic science and translational research, genetic susceptibility and prevention, diagnostic imaging, screening and diagnosis and, finally, therapy. Unfortunately, at present, results of treatment are still far from optimal. Integration of surgery with chemotherapy are crucial in the treatment of ovarian cancer and the recommended treatment strategy for patients with advanced ovarian cancer is radical cytoreductive surgery followed by 6 cycles of platinum-based combination chemotherapy [2]. The role of whole-abdominal radiation therapy in the treatment of ovarian cancer is still controversial. In particular, evidence that radiation therapy is curative in patients with advanced disease is lacking while severe toxicity is reported [3]. Critics of this modality have argued that the dose of radiation that can be safely delivered is low and unlikely to eradicate more than microscopic disease.

Despite the fact that during the last two decades the cytoreductive ability of gynaecological oncologists has increased and an higher response rate to platinum-based chemotherapy can be obtained, the state of the art treatment fails to cure the vast majority of patients with advanced disease. In order to minimise the tumour burden before chemotherapy, cytoreductive (or debulking) surgery is usually performed upfront. Possible benefits from upfront cytoreductive surgery include: (a) improvement of tumour response to further therapy due to improved tumour perfusion and increased growth fraction. Smaller tumour masses require fewer cycles of chemotherapy with less chance of induced drug-resistance. Clones of phenotypically resistant cells may be removed also; (b) immediate treatment, or prevention of complications arising from tumour masses, i.e. bowel obstruction and ascites; (c) enhancement of the immunological competence of the patient. The immunogenicity of ovarian cancer has been demonstrated in vivo and cytoreduction may help the patient to mobilise her own immune response to the cancer [4]; (d) psychological benefit to the patient of knowing that the tumour bulk has been removed [5].

Several non randomised studies showed improved survival of patients with less than 1 cm diameter of residual tumour after primary surgery, as compared with patients with larger lesions. In a case-control study of patients with minimal residual disease, Eisenkop et al. reported a longer survival for patients whose small lesions were completely resected rather than for those patients whose similar lesions were not completely removed [6]. Conversely, both Hoskins [7] and Hacker [8] reported that, despite optimal cytoreduction, the survival of patients with large intra-abdominal metastases before resection was significantly worse than that observed in patients with initially small intra-abdominal lesions. These observations suggested that intrinsic tumour factors are of prognostic importance in addition to residual disease after cytoreduction and also raised the question of whether cytoreduction has a significant effect on survival among patients with the same size tumours and the same intrinsic prognostic factors. Moreover, the problem still under debate is whether the observed survival benefits for cytoreduced patients are a function of surgical skill, tumour biology or both.
Indirect evidence is available that shows that inherent tumour biology relates to resectability. In the past twenty years, indeed, the definition of an 'optimal debulking' has changed many times, from a largest residual tumour mass of less than 2 cm to no residual disease. An optimal debulking has been shown to provide a median survival of 39 months compared with 17 months for patients who did not reach an optimal cytoreduction [9].

The value of debulking surgery after induction chemotherapy has been largely debated in the last decade. Recently, several studies supported the rationale for introducing the concept of 'interval debulking surgery' meaning a "surgical procedure with debulking intent preceded and followed by cytoreductive chemotherapy" even if its value has been difficult to assess. Some studies, indeed, suggested that patients in whom cytoreduction was optimal after induction chemotherapy had approximately the same survival rate as patients in whom cytoreduction was optimal at primary surgery [10,11]. Other authors, however, reported just the opposite [12,13]. Patients with optimal cytoreduction at intervention surgery had indeed poorer rates of survival than patients with optimal cytoreduction at primary surgery. Moreover, the survival of patients with optimal cytoreduction at intervention surgery was the same as that of patients with suboptimal cytoreduction. All these studies, albeit including only small numbers of patients and retrospective, constituted the rationale for the only prospective randomised study on 'interval debulking surgery' which was performed by the EORTC. Gynecological Cancer Cooperative Group and completed in 1993 [14]. In this trial, patients who underwent primary cytoreductive surgery but could not be optimally debulked (residual tumour lesions >1 cm) were evaluated after three courses of cyclophosphamide 75 mg/m² plus cisplatin 75 mg/m² (CP), given with 3-week intervals. Those not progressing after three courses (NC, PR, CR) were randomised to receive either three more courses of CP (control arm, n = 138) or to undergo exploratory laparotomy for interval debulking surgery followed by three courses of CP (investigational arm n = 140). Overall, a survival advantage was demonstrated for patients who underwent interval debulking surgery with persisting lengthening of progression-free interval of 6 months and a 33% reduction of probability of dying of disease at 2 years. A confirmatory trial is ongoing within the Gynecologic Oncology Group in the USA. However, the chemotherapy used in that study consists of paclitaxel, given at a dose of 135 mg/m² over 24 hours plus cisplatin 75 mg/m², the regimen as used in the original GOG protocol #111 (see chapter on first line therapy).

Based on the above reported data one could conclude that also primary surgery tumour reduction, even when in patients with suboptimal cytoreduction, results in a survival benefit. Nevertheless, while planning the better integrated chemosurgical treatment for a patient suffering from advanced ovarian cancer one should also be concerned about the number of surgical procedures to be employed in order to reach the longer survival. Indeed, a 'primary laparothomic procedure' — with diagnostic and often debulking intent — followed by an 'interval debulking surgery' — with optimal debulking intent — after three courses of chemotherapy and, finally, in selected instances (i.e. patients enrolled in prospective phase III multicentre clinical trials) a 3rd-look surgical procedure (either laparotomic or laparoscopic) might have an adverse impact at least on patient's quality of life during and after a 4-month period of time in which cytotoxic chemotherapy is administered. For that, but not only for that, reason, in the more recent years neoadjuvant chemotherapy has been proposed for patients with established bulky disease (stage III C) [15,16]. In one retrospective study the survival of a group of patients with advanced ovarian carcinoma treated with neo-adjuvant chemotherapy when unfavourable characteristics were present was similar to a former series treated at the same institution with 'optimal debulking' (<1.5 cm) in 89% of the patients [9] suggesting that the same survival with lower operative morbidity could be obtained throughout a chemical upfront debulking compared with a surgical one.

Nelson proposed computerised tomography criteria to predict resectability to an optimal status in patients with suspect ovarian masses [17] that could be used as an alternative to (or in association with) an (open) laparotomy [18] to confirm the diagnosis and to evaluate operability. As an alternative to the laparoscopic procedure, albeit in association with Nelson's criteria, a fine-needle biopsy — imaging guided — might be employed in order to confirm the diagnosis of epithelial ovarian cancer.

The EORTC Gynecological Cancer Cooperative Group has recently initiated a randomised phase III study (protocol no. 55971) comparing upfront debulking surgery versus neoadjuvant chemotherapy in patients with stage IIIc and IV epithelial ovarian cancer in order to compare the two different approaches in terms of survival, progression-free interval and analysing whether the latter approach might result in a lower postoperative morbidity and overall improved quality of life. After an intraperitoneal biopsy (imag-
ing-guided or laparoscopically taken) confirming an epithelial ovarian cancer with disease larger than 2 cm, eligible patients are randomised between upfront cytoreductive surgery followed by three courses of platinum-paclitaxel based chemotherapy followed by interval debulking surgery, when indicated, and another three courses of the same chemotherapy (arm A) versus upfront chemical debulking represented by three courses of chemotherapy (as in arm A) followed by interval debulking surgery in all patients with response or stable disease and another three courses of the same regimen (arm B). With an accrual time of 4 years and a minimum follow up of 3 years more than 700 patients will be required in order to show equivalence or a statistically significant difference between the two treatment arms. Only senior surgeons will be allowed to have the responsibility for the treatment following precise surgical guidelines. Each institution participating in the trial will have to declare their policy regarding second-look at the end of planned treatment. The EORTC core questionnaire QLQ-c30 will be used to assess quality of life in terms of physical, psychological and social aspects.

In conclusion, after much debate concerning the identification of the most appropriate timing of surgery for advanced epithelial ovarian cancer and the more recent data in literature concerning 'resection versus resectability' the following points can be made.

(a) The strong correlation between chemosensitivity, successful debulking surgery, and survival very strongly support the concept that it is the biological characteristics of the tumour that allow the patient to have successful cytoreductive surgery rather than the aggressiveness of surgery itself.

(b) Interval debulking surgery after three courses of platin-based chemotherapy has proven to be effective in prolonging both progression-free interval and overall survival in patients with sub-optimal cytoreductive surgery upfront.

(c) The main concern regarding interval debulking surgery to be applied in all instances is regarding morbidity of two major surgical procedures integrated within a short period of time in which also cytotoxic chemotherapy is administered.

(d) Neoadjuvant chemotherapy has been proposed in patients with bulky disease with the following 3 theoretical advantages: improvements of the patient's performance status prior to the operative procedure; reduction in tumour volume, ascites, pleural effusion and improved oral intake; and increased rate of optimal cytoreduction which may translate into an improvement in survival and may reduce the morbidity of surgical debulking (avoidance of bowel surgery, lower blood loss, shorter operating time and hospital stay).

(e) A prospective phase III randomised trial has been undertaken by the EORTC–GCCC in order to verify the conceptual advantages of a chemical versus a surgical upfront debulking procedure in advanced ovarian cancer. Neoadjuvant chemotherapy in no way obviates the concept of cytoreductive surgery, but should be viewed as cytoreductive chemotherapy prior to definitive cytoreductive surgery.

References


