

The management of epithelial ovarian cancer: neoadjuvant chemotherapy and interval surgery

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Ovarian cancer is the fourth most common cause of death from cancer in women and remains a significant problem. Treatment continues to be difficult as most women have advanced stage cancers at presentation. Some progress in terms of management and survival has been made in the last 20 years, but the mortality rate remains high. Improving outcomes in terms of mortality and quality of life will rely on a better understanding of the aetiology, effective population screening and increased management options.

The aetiology of epithelial ovarian cancers is largely unknown but hormonal, environmental and familial factors are known to play a role. Known genetic factors play a role in about 10% of ovarian cancers, with mutations in BRCA1, BRCA2 and mismatch repair genes making up about 90% of these cases. A better understanding of the prognosis, chemosensitivity and the use of novel agents, such as poly ADP ribose polymerase (PARP) inhibitors in women with BRCA mutations, will result in more tailored treatments in the future. Management based on microarray studies and molecular selection may also improve responses and decrease the side effects of treatments in the future. Effective screening would be a significant step forward but, despite ongoing research, currently population screening and surveillance of high risk women with transvaginal ultrasound and tumour markers has been unsuccessful. There is a need to increase the number of surgical options in an effort to not only improve survival but also to reduce morbidity. Until recently, the surgical treatments have been largely based on non-randomised studies.

For the present, the standard management of ovarian cancer recommends performing primary debulking surgery as soon as possible in the course of the patient's treatment, followed by adjuvant chemotherapy.

Primary debulking surgery aims to reduce macroscopic tumour to nil or, at most, 1cm nodules. The theoretical rationale for this approach is that any remaining tumour

will have improved tumour perfusion and an increased growth fraction, resulting in an increased response to chemotherapy. The physiological benefits to the patient of decreased tumour bulk and ascites, resulting in an improvement of intestinal function, nutritional status and symptoms, are also cited. For now, primary surgery remains the treatment of choice, followed by six cycles of carboplatin and paclitaxel. But how much surgery should be performed to achieve this optimal debulking? The more radical the surgery, the greater the potential for surgical morbidity and mortality. Some stage IIIC cancers can be optimally debulked with relatively simple surgery, but others may require very radical surgery involving bowel resections, stomas, mobilisation of the liver with stripping of the diaphragmatic peritoneum and other procedures, because of the site and invasiveness of the tumour. What good evidence is there that this sort of maximal effort improves survival? The literature abounds with retrospective evidence and conflicting results over the last 40 years. Tumour biology, the extent of surgery, histopathology and non-randomised trials have played confounding roles when assessing outcomes. Mucinous and clear cell carcinomas are also independent predictors of poor prognosis in Stage III and IV epithelial ovarian cancers. The rate of optimal cytoreduction also varies amongst surgeons, with some more capable or willing than others to provide a maximal surgical effort whatever or however long it takes. The concept of primary surgery is now being challenged by the increasing acceptance of neoadjuvant chemotherapy and interval surgery.

Interval surgery after three cycles of neoadjuvant chemotherapy is increasingly being practised for large difficult to remove Stage III cancers and the Stage IV cancers. The results of two large randomised studies, the Chemotherapy or Upfront Surgery (CHORUS) and European Organization for Research and Treatment of Cancer (EORTC) 55971, are awaited. Preoperative diagnosis, survival and quality of life issues are

being studied. The preliminary findings for the EORTC study seem to indicate similar outcomes when compared to primary surgery, but reduced morbidity and possibly a better quality of life. The published findings are expected later in 2010.

Apart from outcomes in terms of survival and quality of life, other important comparative issues before the acceptance of interval surgery includes the pretreatment diagnosis of ovarian cancer and the prediction of resectability of tumour primarily or after neoadjuvant chemotherapy.

Primary surgery allows a definitive histological diagnosis. Before neoadjuvant chemotherapy, a diagnosis of epithelial ovarian cancer by several other methods has been suggested: diagnostic laparoscopy, core biopsy histology and immune staining and ascitic or pleural fluid or fine needle aspiration cytology. When performed, cytology has been shown to be reliable in over 95% of cases. Clinical factors alone, or in combination with a normal colonoscopy result, may be insufficient for management or enrolment on clinical trials.

A clinical model that can predict which patients will undergo optimal cytoreduction, whether primary or interval, would be very useful. At present, no such model exists. More research is needed to devise a set of uniform criteria that can be used to predict ovarian cancer resectability among different patient populations. Imaging criteria using computed axial tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning has been attempted. The presence of gross ascites often indicates widespread peritoneal disease and a decreased chance of optimal primary debulking. A good response from neoadjuvant chemotherapy is required before proceeding with interval surgery. A significant reduction in tumour size and ascites after three cycles of chemotherapy would encourage continuing with interval surgery. CA-125 response has also been shown to be an independent prognostic factor which strongly predicts for optimal interval cytoreduction. It has also been suggested that, if primary surgery by a trained subspecialist gynaecological oncologist has failed to achieve optimal cytoreduction, then optimal interval surgery is also unlikely. Is this more potential confusion from retrospective data?

To date, there is very little good quality evidence to either support or refute the use of neoadjuvant chemotherapy in the treatment of ovarian cancer. There will always be a place for primary surgery, but interval surgery is set to play an important and increasing role in the management of epithelial ovarian cancer. Randomised controlled trials are important if we are to make progress and avoid the confusion and mistakes of the past.

Author's note: The EORTC study referred to in this commentary was published in September: Vergote I, Tropé CG, Amant FA, et al. Neoadjuvant chemotherapy or primary surgery in Stage IIIC-IV ovarian cancer. *N Engl J Med* 2010;363:943–953.

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