Recent EORTC and MRC UK studies: implications for imaging ovarian cancer

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Abstract
For many years the primary management of newly diagnosed advanced ovarian cancer has been cytoreductive surgery followed by chemotherapy, and the mainstay of follow-up of treated women has been serial assay of serum CA-125. The findings of 2 recent research protocols have a significant effect on these aspects of management.

Keywords: Ovarian cancer.

Introduction
A significant minority of women with newly diagnosed ovarian cancer are unfit for radical surgery or the outcome of multidisciplinary review is that surgery is unlikely to adequately debulk their extensive tumour. For this group, neoadjuvant chemotherapy is increasingly being used as the primary treatment with the aim of proceeding to subsequent surgery should the patient and/or disease bulk improve sufficiently to allow this. This protocol of neoadjuvant chemotherapy followed by interval debulking surgery (IDS) was described in an EORTC study reported in 1995 [1].

That approach is being further investigated in the EORTC 55971 study and the MRC UK CHORUS (Chemotherapy OR Upfront Surgery) study. These studies address the timing of surgery relative to chemotherapy for newly diagnosed ovarian cancer and women believed to be suitable for surgery at diagnosis were randomised to receive either surgery followed by chemotherapy or neoadjuvant therapy followed by IDS. Early results from the EORTC 55971 study indicate similar outcomes for the 2 randomised arms but lower surgical morbidity in the IDS arm. The CHORUS study is continuing to recruit and an a priori plan is for meta-analysis of the 2 studies.

The management implications of these studies are significant: at first sight the pivotal role of surgery in initial management is challenged. There has been much debate and some criticism of the study findings and recommendations but it seems clear that 'use of neoadjuvant chemotherapy is a safe alternative in this group of patients and does not compromise the standard of care'. There are also significant implications for imaging and investigation of these women with suspected ovarian cancer. Embarking upon neoadjuvant chemotherapy demands a confident histological diagnosis and this can be provided by image-guided core biopsy (IGCB) [2–4]. This becomes more important as investigation of chemotherapy regimens specific to the different subtypes of ovarian cancer are being established. Put simply, a diagnosis of adenocarcinoma based on cytological evaluation of ascitic fluid is increasingly insufficient. Other cytological techniques such as preparation of a cell block specimen are untested in this regard.

One tantalising question for future investigation is whether women could be treated by chemotherapy alone. In the IDS protocol, women are treated with 3 cycles of chemotherapy, re-evaluated with computed tomography (CT), undergo surgery and then complete their chemotherapy with 3 or more further cycles of treatment. Some women have such an impressive response to the initial 3 cycles of therapy that no residual disease is
evident on the re-evaluation CT. The question has often been asked in our own multidisciplinary team meetings (MDTM) as to the purpose of removal of the apparently normal gynaecological apparatus and omentum at that stage. The surgery potentially interrupts the intensity of chemotherapy and/or causes morbidity in a woman who is starting to feel well again.

The more recent joint EORTC 55955/MRC UK OV05 study addresses another key question: what is the value of treating recurrent ovarian cancer diagnosed by CA-125 assay versus treating women who relapse clinically? It has been known for many years that CA-125 levels increase weeks or months before there is any clinical or CT scan evidence of disease. In the above protocol, women with treated ovarian cancer who were in complete remission were followed up with clinical review including CA-125 measurements. Neither the doctor nor the patient saw the results until they became abnormal. At that point the patients were randomised to be informed and treated with rechallenge chemotherapy or not to be informed and for chemotherapy to be withheld until there was clinical or imaging evidence of recurrent disease. This joint study had large patient numbers: 529 women were randomised.

The results of this study were recently presented at the plenary session at the 2009 ASCO meeting[5]: the women treated in the 2 arms had no difference in survival but the patients in the CA-125 triggered arm had cumulatively received more cycles of chemotherapy, were treated about 5 months earlier for both second and third line therapies, and appeared to have worse quality of life score as judged by time to deterioration following randomisation. Arguably this resulted from the administration of chemotherapy.

The MRC has been quick to advise women about the implications of OV05[6]. It has stated that women can be reassured that:

1. there is no benefit from early detection of relapse by routine CA-125 measurements, and
2. even if CA-125 increases, chemotherapy can be safely delayed until there are symptoms or signs of tumour recurrence.

MRC has recommended that women should be offered an informed choice in follow-up either to have no routine CA-125 measurements but rapid access to CA-125 testing if there are symptoms or signs of relapse or to have regular CA-125 measurements as is currently the case. Imaging has had no place in routine follow-up of women with treated ovarian cancer but is used responsively to an increased or increasing CA-125 level or to investigate symptoms suggestive of relapse. It now seems inappropriate to image any woman simply on the basis of CA-125 data. A variety of strategies have been suggested for the CT negative CA-125 positive woman ranging from recommencing chemotherapy to seeking imaging or other confirmation of the relapse. Interval reassessment with CT, after say 3 months, is one option for the asymptomatic woman but alternatives tested include positron emission tomography (PET) or PET-CT. Several studies have demonstrated the superiority of PET-CT over conventional diagnostic CT for the diagnosis of suspected ovarian cancer recurrence but its greatest utility is in the setting of the patients with increasing CA-125 levels and negative conventional imaging[7]. The EORTC 55971/OV05 study results suggest that use of these expensive and still scarce resources may not be justified for the asymptomatic woman.

There is one small group of women with ovarian cancer for whom use of CT in follow-up had been thought appropriate. About 1 in 10 women are marker negative (MN) at diagnosis, i.e. they do not have increased CA-125 levels. Our own policy has been to offer these women the option of CT follow-up but the OV05 results suggest that in future we might safely rely upon symptoms to trigger reinvestigation.

In summary, the results of these collaborative studies from EORTC and MRC UK are likely to have a significant effect on the management of ovarian cancer. More image-guided biopsies are likely if IDS increases in popularity. CT evidence of recurrent tumour may become the standard of proof required for treatment of recurrent disease.

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