Review Management of early-stage epithelial ovarian cancer

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Key content:
• Approximately 30% of women presenting with epithelial ovarian cancer will have early-stage (stage I) disease.
• The multidisciplinary team is central to deciding the optimal management for these women.
• Comprehensive surgical staging is important in determining the need for chemotherapy.
• Although the combined ACTION and ICON 1 studies of chemotherapy showed an improved overall survival, both included large numbers of incompletely staged women.

Learning objectives:
• To understand the problems in diagnosing early-stage ovarian cancer and the need for referral to a multidisciplinary team in deciding on management.
• To understand the importance of correct surgical staging and the possible need for chemotherapy.
• To gain an understanding and awareness of the role of minimal access surgery and fertility-sparing surgery.

Ethical issues:
• Difficulties in diagnosing early-stage ovarian cancer can lead to incomplete staging and, ultimately, have a negative effect on prognosis.

Keywords chemotherapy / diagnosis / early-stage ovarian cancer / multidisciplinary team / surgical staging
Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynaecological cancer in the UK. The cancer is confined to the ovaries in approximately 30% of women at diagnosis, corresponding to FIGO stages IA to IC (Table 1); this is termed ‘early-stage ovarian cancer’.4 Despite the apparently limited extent of the disease, up to 50% of women with early-stage ovarian cancer will develop a recurrence and 20–30% will die from the disease.2,4 Attempts have been made to identify prognostic factors to differentiate those women who would benefit from chemotherapy.6

In the UK, gynaecological cancer services are organised into cancer networks consisting of cancer units and cancer centres. Women with features suggestive of ovarian cancer should be referred to a centre with a gynaecological oncology multidisciplinary team of gynaecological oncologists, medical oncologists, pathologists, radiologists and nurses. Evidence suggests that such referral is associated with an improved prognosis.2,4 In many women with advanced EOC the diagnosis is relatively straightforward and based on the findings of ascites, a pelvic mass and a raised level of the serum tumour marker CA125. Women with suspected early-stage ovarian cancer should be referred to the multidisciplinary team for discussion and to determine the correct initial management. This should allow individual tailoring of the woman’s treatment. Ovarian cysts or masses are assessed for the likelihood of cancer by risk-of-malignancy indices. These formulae commonly combine the menopausal status of the woman, the serum CA125 level and the ultrasound or radiological features of the lesion. Their reported sensitivity ranges from 71–80% and specificity from 92–96% for all EOC.6 Risk-of-malignancy indices are less likely to classify early-stage ovarian cancer as abnormal for several reasons:

- women with stage I disease tend to be younger
- 50% will have a normal serum CA125 level13
- ultrasound or radiological features can appear benign.

Many general gynaecologists will, therefore, continue to operate on women with early-stage ovarian cancer.

There is no screening programme currently; however, screening for early-stage ovarian cancer in a low-risk population of 200 000 women is being studied in the UK Collaborative Trial of Ovarian Cancer Screening. This is a randomised controlled trial using combinations of transvaginal ultrasound scanning and serial serum CA125 measurements compared with a control arm.10 The primary endpoint of this study is ovarian cancer mortality.

Surgical management of suspected stage I ovarian cancer

The standard management of all women with suspected EOC is a staging laparotomy. This should include:

- washings of the peritoneal cavity
- total abdominal hysterectomy and bilateral salpingo-oophorectomy
- infracolic omentectomy
- selected lymphadenectomy of the pelvic and para-aortic lymph nodes
- examination of the diaphragm, right and left abdomen and pelvis, with biopsy of any suspicious lesions, masses and appendicectomy for mucinous tumours.12

The aim of debulking surgery is to remove all macroscopic disease: data suggest that this results in improved survival.13,14 Approximately 25% of women with apparent early EOC will have more advanced disease if fully staged and this may explain the higher than expected recurrence rates in this group.6 Several clinical prognostic factors have been identified in early-stage EOC: these include the tumour grade and type and the presence of ascites. Women with stage IA and IB grade 1 tumours have an excellent prognosis, with a 5-year survival rate of around 90%.11 Women with clear cell tumour type, positive pelvic washings or tumour rupture during surgery are considered to be at high risk of recurrence.15

Adjuvant treatment

Three small, randomised controlled trials (RCTs)16,17 addressed the question of whether adjuvant chemotherapy is of benefit in early EOC. One study16 reported an improved recurrence-free interval but all three failed to show any survival benefit with chemotherapy. These small-scale studies lacked the power to detect anything less than a very large survival difference.

Two large RCTs18,19 concerning the benefit of chemotherapy in early-stage EOC were published in 2003 (Table 2).

The ICON1 study

The ICON1 study20 involved 477 women in whom it was unsure whether chemotherapy would be of benefit. Details about the extent of surgical staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Growth limited to ovaries</th>
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<tbody>
<tr>
<td>IA</td>
<td>Growth limited to one ovary; no tumour on external surface and capsule intact; no malignant cells in ascites</td>
</tr>
<tr>
<td>IB</td>
<td>Growth limited to ovaries; no tumour on external surface and capsule intact; no malignant cells in ascites</td>
</tr>
<tr>
<td>IC</td>
<td>Tumour either IA or IB but with tumour on the surface of one or both ovaries; or capsule ruptured; or with ascites containing malignant cells or with positive peritoneal washings</td>
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</table>
are not available, but it is likely that many of the women included were not optimally staged. Chemotherapy was given over six cycles and a significant difference in disease-free survival (73% versus 62%) and 5-year overall survival (79% versus 70%) was found in favour of chemotherapy.

The ACTION study
The ACTION study\(^2\) involved 448 women randomised to observation or four cycles of chemotherapy. Approximately 66% of the women were suboptimally staged by FIGO criteria, suggesting that a number would have had occult stage III disease. There was a significant difference in disease-free survival in favour of chemotherapy (76% versus 68%) but no significant difference in 5-year overall survival was reported (85% versus 78%). Unplanned retrospective analysis of the trial data suggested that there was no significant difference in disease-free survival or overall survival for optimally staged women. It should be understood that this subgroup analysis was underpowered to detect anything less than a large difference.

A combination of the trials confirms the benefit in terms of disease-free interval and 5-year survival of chemotherapy over observation in the population studied.\(^2\) Considerable controversy exists over the practical implications of these two studies. Should all women with early-stage EOC receive chemotherapy or just those who are incompletely staged? Previous evidence suggested that women with stage IA and IB grade 1 disease have an excellent prognosis without further treatment but that women with stage IC disease may well benefit from chemotherapy. It is difficult to decide the best management for women with stage IA grade 2 and stage IB grade 2 who have been completely staged by FIGO guidelines. The ICON 1 and ACTION studies are unable to answer this question.

Laparoscopic management of suspicious ovarian cysts
Minimally invasive techniques have gained popularity for the treatment of ovarian cysts. These techniques offer advantages such as an earlier discharge and return to day-to-day activities than for traditional techniques. If malignancy is considered a possibility, the laparoscopic surgeon should obtain pelvic washings at the beginning of the procedure. Intentional rupture or open aspiration of any cyst should be discouraged. This can lead to problems with ovarian cyst removal through 10–11 mm incisions. Cysts can be placed within an endoscopic bag and aspirated within the bag to facilitate removal (Figure 1 and Figure 2). Alternatives include extension of the suprapubic port site or removal of the cyst through an incision in the pouch of Douglas.

The appropriateness of the laparoscopic approach in the initial management of women with ovarian cancer is unclear. Obvious spread of disease beyond the ovaries (FIGO stages II–IV) should prompt conversion to a full staging laparotomy. It may, therefore, be prudent to abandon the operation after performing a biopsy and refer the woman to a gynaecological oncology centre. Potential risks of laparoscopic surgery for stage I cancer include understaging and dissemination of the malignancy. Laparoscopic surgery for a suspected stage I ovarian cancer should include bilateral salpingo-oophorectomy with laparoscopically assisted vaginal hysterectomy combined with infracolic omentectomy, pelvic and para-aortic node sampling plus appendicectomy. This requires a high degree of training in oncological and laparoscopic surgery. The largest series to date on the surgery and outcome of laparoscopic management of stage I disease consisted of 24 women.\(^2\) Comprehensive staging was performed laparoscopically in all women, with no major intraoperative complications. Two women developed a recurrence and survival was 100% over a mean follow-up of 46.4 months. It is difficult to draw firm conclusions from a small non-comparative study size. Entry criteria Staging surgery Overall 5-year survival Disease-free survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Study size</th>
<th>Entry criteria</th>
<th>Staging surgery</th>
<th>(chemotherapy versus observation) +</th>
<th>(chemotherapy versus observation) +</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON1</td>
<td>477</td>
<td>Unsure if chemotherapy required</td>
<td>Not clear, but likely that the majority were not fully staged by FIGO guidelines</td>
<td>79% versus 70% (P= 0.03)</td>
<td>79% versus 62% (P= 0.01)</td>
</tr>
<tr>
<td>ACTION</td>
<td>488</td>
<td>Stage IA–IB, grades 2–3</td>
<td>Two-thirds not fully staged by FIGO guidelines</td>
<td>85% versus 76% (P= 0.10)</td>
<td>76% versus 68% (P= 0.02)</td>
</tr>
<tr>
<td>Combined</td>
<td>925</td>
<td>Clear cell type</td>
<td></td>
<td>82% versus 74% (P= 0.008)</td>
<td>76% versus 65% (P= 0.001)</td>
</tr>
</tbody>
</table>

Table 2 Results of the ICON1 and ACTION randomised controlled trials\(^2,3\)
study but it does suggest that laparoscopic staging is possible.

There are further reservations about the use of laparoscopy in women with ovarian cancer. A carbon dioxide pneumoperitoneum has been reported to lead to tumour dissemination in animal models. In vitro exposure to carbon dioxide for 3 hours induced accelerated growth in one ovarian tumour cell line. By contrast, however, clinical data from 289 women with advanced ovarian cancer were analysed to compare survival rates between second-look laparoscopy with second-look laparotomy and no survival difference was found.

Port site metastases have been reported in 1–20% of women with ovarian cancer. These studies have concentrated on women with advanced disease and it seems unlikely that women with unruptured stage I disease with negative washings are at significant risk.

Fertility-sparing surgery

The risk of EOC during a woman’s reproductive years is low. The chance that an epithelial ovarian tumour is malignant or borderline in a woman under 40 years of age is around one in 10. Ovarian cysts or masses in this age group are much more likely to be due to benign causes such as functional cysts or endometriosis and can be associated with a raised serum CA125. The relative increased risk of germ cell tumours in this group of women means that other serum tumour markers should be measured, including alpha-fetoprotein, beta-human chorionic gonadotropin and lactate dehydrogenase.

In women with a suspicious complex ovarian cyst or mass who wish to conserve their fertility it would be reasonable to offer a unilateral oophorectomy combined with surgical staging. The majority of these cysts will be endometriomas, benign cystadenomas, borderline tumours or germ cell tumours (including mature teratomas). Frozen section analysis of abnormal ovarian lesions appears to be helpful. A study of 130 women with suspicious masses reported a sensitivity of 97%, specificity of 95%, positive predictive value of 90% and negative predictive value of 99% for malignancy. This study included 34 cases of early-stage ovarian cancer and excluded non-ovarian lesions. The use of frozen section analysis should avoid unnecessary staging surgery in 99% of women with benign lesions but should identify 90% of women who would benefit. A unilateral oophorectomy combined with surgical staging would normally be considered optimal primary treatment for borderline or germ cell tumours. Women with stage IA and IB cancer with low-risk features are not offered chemotherapy. Women with high-stage grades IA–IB or any stage IC are normally offered chemotherapy, with possible loss of fertility. The effect on fertility of chemotherapy drugs such as platinum agents and taxanes is not well established. The fertility effect of alkylating agents in breast cancer is age-dependent and this suggests that the degree of ovarian reserve is important.

Women should be fully aware that declining adjuvant treatment can affect their prognosis but they may wish to accept this risk to conserve their fertility. Unfortunately, the medical literature on the subject is limited. Several retrospective small-scale studies have been published, with numbers ranging from 10 to 56. One of these studies retrospectively compared 56 women who underwent fertility-sparing surgery with 43 women treated with full FIGO staging for early-stage ovarian cancer. Recurrence rates were similar (9% versus 12%) in both groups. In addition, microscopic involvement of a normal-looking contralateral ovary is rare in stage I ovarian cancer, with a reported frequency of 2.5% in a study of 118 women with early-stage ovarian cancer after full FIGO staging.

Conclusion

Approximately 30% of ovarian cancer is confined to one or both ovaries at presentation. Correct staging, in keeping with FIGO recommendations, is critical in identifying women who would benefit from chemotherapy. This can be a matter of life or death, as a quarter of women with apparent early disease will be upstaged. Rupture or open aspiration should be avoided if a suspicious cyst is managed laparoscopically. Instead, aspiration in a closed bag, with removal of the cyst through the abdominal wall port, appears to be beneficial. Laparoscopic staging is feasible but should be reserved for suspected early stage disease because of concerns regarding port site metastases. The success of any future screening programmes for ovarian cancer will depend on detecting the malignancy at an early, and therefore potentially
curable, stage. The use of minimal access surgery may reduce the morbidity associated with the number of operations required to diagnose and treat a woman with ovarian cancer.

References


