Ovarian cancer: current management and future directions

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Abstract
Ovarian cancer has the highest mortality of all the gynaecological malignancies. Epithelial ovarian cancer is the most common subtype. Approximately 5–10% occur in women with an inherited predisposition. These patients may benefit from prophylactic surgery. Diagnosis involves measurement of CA 125 and ultrasound. The results of both are combined to give a risk of malignancy index; this is used to decide where treatment takes place. Treatment of advanced epithelial ovarian cancer usually involves debulking surgery and chemotherapy. The correct order of these treatments is currently being evaluated. There are survival benefits if surgery is performed by a specialist gynaecological oncologist. Current standard chemotherapy for epithelial ovarian cancer is carboplatin with paclitaxel. Treatment may prolong life and palliate symptoms but it is rarely curative. New treatments are constantly being developed and offer the hope of improved outcomes. These include ultraradical surgery, intraperitoneal chemotherapy and novel drug treatments.

Keywords chemotherapy; ovarian cancer; screening; surgery

Introduction
The lifetime prevalence of ovarian cancer in the developed world is 1–2%. It is often described as a silent killer, however the majority of women frequently experience symptoms in the months leading to diagnosis. The majority of ovarian cancers are diagnosed at an advanced stage. In England and Wales ovarian cancer kills more women than all of the other gynaecological malignancies combined.

Pregnancy, breastfeeding and use of the oral contraceptive pill all appear to protect against the development of epithelial ovarian cancer, the lower incidence seen in less developed countries may be related to a higher birth rate.

Patients with ovarian cancer are best managed by multidisciplinary teams. These usually include nurse specialists, medical oncologists, histopathologists, radiologists, palliative care specialists and gynaecological oncologists in collaboration with the patients and their families.

Types of ovarian cancer
Primary ovarian tumour types include epithelial, sex cord-stromal and germ cell tumours. Tumours not specific to the ovaries also occur, such as sarcomas and lymphomas. Metastatic tumours from breast, stomach and endometrial primaries are not uncommon.

Epithelial tumours
More than 80% of ovarian cancer is epithelial in origin. The most common subtype is serous, accounting for about 50%, followed by endometrioid, mucinous, clear cell, transitional (Brenner), mixed and undifferentiated tumours. These have previously been treated as essentially the same disease with differing histology; however, it is becoming increasingly evident that they behave as distinct entities. For example, endometrioid and clear cell cancers are strongly linked with endometriosis, whilst many mucinous cancers originate in the appendix and evidence increasingly points to serous tumours arising from dysplastic endometrium in the distal fallopian tube. Response to chemotherapy varies, serous tumours tend to be highly chemosensitive, but clear cell and mucinous tumours are more resistant to conventional chemotherapy.

Primary peritoneal cancer is histologically indistinguishable from metastatic serous ovarian cancer. It is diagnosed in the absence of any clear ovarian primary. Treatment is the same as for ovarian cancer, although, as there is often no mass to debulk, chemotherapy is more often used as the primary treatment.

Borderline ovarian tumours are not truly cancers but are termed “borderline” because they show histological features that are intermediate between benign and malignant tumours. They are staged in exactly the same way and sometimes spread beyond the ovary to produce non-invasive implants in the omentum and the peritoneum. They can recur after long periods, cases have been documented with disease returning over 30 years after the initial presentation. They are typically found in a younger population than epithelial cancers, one third occur in women under the age of 40. The main treatment is surgical excision and opinions differ in the extent of surgery required. It is probable that they represent premalignant disease for low grade ovarian carcinomas.

Sex cord-stromal tumours
Sex cord-stromal tumours account for approximately 7% of all malignant ovarian tumours. They arise from a combination of the hormone producing cells of the ovary and stromal fibroblasts. 70% of all malignant sex cord-stromal tumours are granulosa cell tumours. The majority occur in women in their sixth decade, although a small proportion arise in young women and prepubertal girls. Granulosa cell tumours may secrete sex hormones, most secrete oestrogen (although androgen secreting varieties do occur) potentially leading to endometrial hyperplasia and carcinoma. Presenting symptoms include abdominal distension, acute abdominal pain and abnormal vaginal bleeding. As most present at an early stage the prognosis is good. Treatment is principally surgical with platinum-based chemotherapy for advanced disease. Surgical treatment is as for epithelial ovarian cancer although in young women with early disease fertility preservation is an option. Other stromal tumours are rare and include thecomas, fibromas, Sertoli–Leydig cell tumours and gynandroblastomas.
Malignant germ cell tumours
Malignant germ cell tumours occur chiefly in girls and young women. The most common variety is the dysgerminoma, the counterpart to the seminoma in the male. Other types include the yolk sack tumour, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma and teratoma. They usually present with abdominal pain, which is sometimes acute, and a palpable pelvic mass. Treatment for early stage disease is surgical. As over 60% are confined to one ovary at diagnosis, fertility sparing surgery is usual with unilateral salpingo-oopherectomy or even ovarian cystectomy in selected cases with otherwise normal ovaries. Dysgerminomas are highly radiosensitive but platinum-based chemotherapy is currently the preferred option as radiotherapy usually results in premature ovarian failure. Non-dysgerminoma tumours are treated with the chemotherapy combination of bleomycin, etoposide and cisplatin. Response rates are excellent with cure rates approaching 100% in early stage disease and up to 75% in advanced disease.

Familial ovarian cancer
Approximately 5–10% of all ovarian cancer is associated with a genetic predisposition. Individuals carrying these gene defects have a significantly higher risk of developing ovarian cancer than the general population (Table 1).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1.6%</td>
</tr>
<tr>
<td>One 1st degree relative affected under 55 years</td>
<td>5.2%</td>
</tr>
<tr>
<td>One 1st degree relative affected over 55 years</td>
<td>3.4%</td>
</tr>
<tr>
<td>Two 1st degree relatives affected</td>
<td>7%</td>
</tr>
<tr>
<td>BRCA 1 carrier</td>
<td>28–44%</td>
</tr>
<tr>
<td>BRCA 2 carrier</td>
<td>27%</td>
</tr>
<tr>
<td>HNPCC carrier</td>
<td>12%</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer.

Table 1

Biomarkers and screening
The most commonly used marker for ovarian cancer is CA 125 (carbohydrate antigen 125). This is a glycoprotein that is released into the bloodstream by any condition that disturbs the peritoneum, including any peritoneal cancer, cirrhosis, congestive cardiac failure, endometriosis and pelvic inflammatory disease. Pregnancy also causes a variable increase in serum levels. It is therefore notoriously non-specific at low levels. However, serous ovarian cancer can cause dramatic increases in CA 125. This is only likely to occur when the disease has already spread beyond the ovary. Other tumour subtypes, especially mucinous, often produce a more modest elevation.

Other markers are also used. Germ cell ovarian cancers often secrete highly specific tumour markers which are useful in diagnosis and monitoring, e.g. zFP, βHCG and LDH. These should be tested, in addition to CA 125, in women under the age of 40 years with a suspicious pelvic mass. In addition, inhibin may be of use as a marker for mucinous and granulosa cell tumours.

Novel markers are currently under development both as panels and individually. HE 4 (human epididymis protein 4) has been suggested as a biomarker with equal or greater sensitivity and specificity than CA 125, however clinical trials are awaited.

The PLCO (prostate, lung, colon, ovary) trial, a huge US-based randomized controlled trial of cancer screening, has recently reported. It concluded that screening the general population with annual CA 125 and transvaginal ultrasound does not reduce ovarian cancer mortality. Indeed, a significant number of women had major complications from surgery performed because of a false positive screening test.

There are also two large UK based multicentre trials investigating ovarian cancer screening. The first is in postmenopausal women without a significant family history of ovarian cancer and also uses a combination of transvaginal ultrasound and CA 125 (UKTOCS — UK Collaborative Trial of Ovarian Cancer Screening). The second is in women with a significant family history and is testing a panel of biomarkers in addition to CA 125 and transvaginal ultrasound (UKFOCSS — UK Familial Ovarian Cancer Screening Study). Both have now finished recruitment and are due to report in the next few years.

Screening with a combination of CA 125, ultrasound and pelvic examination is commonly performed for anxious patients who desire screening for ovarian cancer. If the findings of the PLCO trial are duplicated in the UKTOCS trial, this practice is likely to become hard to defend in low risk women.

Investigation
The first symptoms of ovarian cancer usually emerge some time before diagnosis. These commonly include early satiety, changes
in bowel habit, bloating, urinary frequency, pelvic and abdominal pain. Patients with advanced cancer often complain of abdominal swelling and discomfort due to ascites +/- a large abdomino-pelvic mass. Eating is often difficult and patients may notice weight loss, apart from the distended abdomen. It is not uncommon for patients to present with a swollen leg secondary to a deep vein thrombosis. However, most small ovarian cancers are asymptomatic when confined to the ovaries and therefore difficult to detect.

Recent NICE guideline recommend that women, especially those over 50 years old, who experience symptoms persistent or frequent symptoms as described above, or new onset symptoms suggestive of irritable bowel syndrome, should have CA 125 measured. If the level is >35 an ultrasound of the abdomen and pelvis should be performed.

The ultrasound and CA 125 together are used to calculate the risk of malignancy index (RMI).

\[
\text{RMI} = U \times M \times \text{CA } 125
\]

\[
U = \text{ultrasound score (1 point for each of multilocular cysts, solid areas, ascites, bilateral lesions, metastases. } \ U = 0 \text{ for 0 points, } \ U = 1 \text{ for 1 point, } \ U = 3 \text{ for 2–5 points).}
\]

\[
M = \text{menopausal status (premenopausal = 1, postmenopausal = 3).}
\]

CA 125 = serum CA 125 level.

A score of 250 has been chosen by NICE to guide triage to either surgery in a cancer centre under the care of a specialist multidisciplinary team, including subspecialist gynaecological oncologists (≥250), or to care under a general gynaecologist with an interest in gynaecological oncology in a cancer unit (<250).

If ovarian cancer is suspected, a CT of the abdomen and pelvis (and thorax if clinically indicated) should be performed, prior to surgery, to assess the extent of the disease.

### Staging

Staging is performed to guide treatment and to provide information on prognosis. Traditionally this has been achieved by performing a staging laparotomy. Information can also be gleaned from radiological investigations, guided biopsy and cytology of ascitic or pleural fluid. The current staging system was devised by FIGO (international federation of obstetrics and gynaecology), see Table 2.

### Treatment

Treatment in ovarian cancer depends upon the stage at presentation and the histological subtype. Non-epithelial cancers are discussed earlier. In general epithelial ovarian cancers are treated with a combination of surgery and chemotherapy. Except in very early disease treatment is rarely curative but it can provide symptom relief and prolong life.

Traditionally ovarian cancer is treated with a staging and debulking laparotomy followed by six cycles of chemotherapy. Second look laparotomy, where a second surgical debulking procedure is performed after completion of chemotherapy, is not beneficial. Data from the EORTC 55971 trial, which compared interval debulking surgery performed midway between six cycles of chemotherapy with the traditional laparotomy and six cycles of post-operative chemotherapy, suggested that neoadjuvant chemotherapy in bulky stage IIIc/IV disease did not adversely affect prognosis and that interval debulking is associated with a lower post-operative morbidity and mortality. The CHORUS (CHemotherapy OR Upfront Surgery) trial also addresses this question and its publication is awaited.

In light of this, interval debulking surgery, performed midway through chemotherapy, is gaining popularity.

### Surgery

Surgical treatment, whether primary or as an interval debulking procedure, involves a midline laparotomy, sampling of ascitic fluid or peritoneal washings for cytology, full assessment by palpation of all peritoneal surfaces and biopsy of any suspicious areas, removal intact of any encapsulated masses or debulking of tumour, sampling of suspicious pelvic and para-aortic lymph nodes, omentectomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy. The aim is to completely remove all visible disease. This is thought to promote an optimum response to chemotherapy. Surgery also provides ample material for diagnostic histological assessment. The evidence for debulking improving chemosensitivity is not absolute. Many argue that the

## FIGO staging of ovarian cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to ovaries</td>
</tr>
<tr>
<td>Ia</td>
<td>One ovary, no ascites present containing malignant cells, no tumour on external surface, capsule intact</td>
</tr>
<tr>
<td>Ib</td>
<td>Both ovaries, no ascites present containing malignant cells, no tumour on external surfaces, capsule intact</td>
</tr>
<tr>
<td>Ic</td>
<td>Tumour limited to one or both ovaries with any of the following: tumour on the surface on one or both ovaries, capsule ruptured, ascites present with malignant cells or positive peritoneal washings</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIa</td>
<td>Extension and/or metastases to uterus and/or fallopian tubes</td>
</tr>
<tr>
<td>IIb</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIc</td>
<td>Tumour stage IIa or IIb but with tumour on surface of one or both ovaries, capsule ruptured, ascites present containing malignant cells or positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumour involving one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis and/or regional lymph node metastasis</td>
</tr>
<tr>
<td>IIIa</td>
<td>Microscopic peritoneal metastasis beyond the pelvis</td>
</tr>
<tr>
<td>IIIb</td>
<td>Macroscopic peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>IIIc</td>
<td>Abdominal implants greater than 2 cm in diameter and/or regional lymph nodes metastasis</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis beyond the peritoneal cavity. Includes liver parenchymal metastasis and/or pleural effusion with positive cytology</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics.

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Table 2
ability to perform optimal cytoreduction is a more a reflection of favourable tumour biology with an intrinsically better prognosis than the surgery itself influencing outcome. However it has been demonstrated that survival in stage III disease is improved by the primary surgery being performed by a specialist gynaecological oncologist, rather than an obstetrician/gynaecologist or a general surgeon.

Surgical aggressiveness varies considerably between continents, countries and individual units. Some studies have shown improvements in survival with radical surgery, including liver resection, bowel resection and splenectomy. Published case series show small or no increases in mortality and morbidity. However, these studies usually involve highly selected cases from single institutions and may not be directly applicable to wider practice. Some disease remains unresectable to even the most adventurous surgeon; this includes small bowel mesenteric disease and disease of the portal triad.

Recent NICE guidance recommends that lymphadenectomy is restricted to removal of clinically involved nodes. Full pelvic and para-aortic node dissection in suspected stage 1 disease is not recommended.

Less aggressive surgery is preferred in early epithelial ovarian cancer in young women who wish to preserve their fertility. About 8% of stage I epithelial ovarian cancers occur in women under the age of 35. A proportion of these will not have completed childbearing and may wish to consider fertility sparing surgery. Suitable patients include those with stage IA, grade 1 or possibly grade 2 disease. Such conservative surgery would typically consist of peritoneal fluid cytology, unilateral salpingo-oophorectomy, omental biopsy and careful inspection of the contralateral ovary and nodal chain. One case series describes 282 women treated conservatively for epithelial ovarian cancer. Just over 30% subsequently went on to have term deliveries. 4% died of conditions related to their disease.

Surgery also plays a role in palliative care of patients with ovarian cancer. Bowel obstruction is common in the end stages of the disease, post-mortem studies of women dying with ovarian cancer revealed bowel obstruction in almost 50%. Before contemplating such surgery consideration must be given as to whether it is appropriate. Surgery should only be performed if it has a reasonable chance of success and risks need to be carefully balanced against potential symptom relief. Contraindications to surgery include patient refusal, rapidly accumulating ascites, high obstruction, multiple levels of obstruction and poor nutritional status. Decisions involving palliative surgery should involve the multidisciplinary team and careful discussion with the patient and her relatives.

Chemotherapy

Patients should have histological confirmation of their ovarian cancer prior to starting chemotherapy. This may be obtained through image-guided percutaneous biopsy, or where this is not possible or the results are inadequate, by laparoscopic biopsy.

The current standard first line chemotherapy regimen for ovarian cancer involves intravenous administration of a platinum based drug with a taxane, usually paclitaxel, given 3 weekly for six cycles. Most units prefer carboplatin to cisplatin as it has a less toxic side effect profile. Evidence for the use of paclitaxel is drawn from its efficacy in relapsed ovarian cancer. However, paclitaxel significantly increases the risk of neuropathy when compared with carboplatin alone and some patients have anaphylactic reactions to taxanes. For these reasons it is not universally used. Chemotherapy can also be given via the intraperitoneal (IP) route, however, currently in the UK its use is not recommended outside of clinical trials.

Epithelial ovarian cancer is one of the more chemosensitive solid tumours and complete clinical and radiological response occurs in up 50% with the above regimen. Conversely 20–30% will show no evidence of response. Unfortunately the majority of patients with advanced ovarian cancer will relapse. Chemotherapy for recurrent disease is determined in part by the length of time before relapse occurs. If it is more than 6 months afterwards it is potentially platinum sensitive and, unless contra-indicated, a regimen containing platinum will be used again. A taxane is likely to be included, especially if not used initially. Paclitaxel is sometimes used at a lower dose at more frequent intervals, this appears to reduce the adverse effects experienced. Response rates are in the order of 30%. If relapse occurs within 6 months, second line drugs, such as liposomal doxorubicin and topotecan, may be considered. As response rates are low, approximately 10–20%, the choice of drug is made bearing in mind side effect profiles and ease of administration.

Novel chemotherapeutic agents are constantly being developed, some of the most promising effect the functioning of vascular endothelial growth factor (VEGF). Interim analysis of the ICON 7 trial of standard therapy with or without bevacizumab (a monoclonal antibody to VEGF) shows a sustained improvement in progression free survival in a subgroup of women with advanced disease and suboptimal surgical debulking.

Hormonal therapies are occasionally used, these probably act by reducing oestrogen activity and include tamoxifen, aromatase inhibitors and GnRH analogues. Response rates of 10–15% have been achieved in relapsed disease. Their main advantage is their minimal side effects when compared with conventional chemotherapy.

Palliative care

Palliation is an integral part of the care of patients with ovarian cancer. Maintaining a balance between optimism and pragmatism, together with knowing when the emphasis of care should tilt towards palliation are some of the most challenging aspects of caring for this group of patients.

Almost all patients with advanced ovarian cancer, whether in the terminal phase or not, will have distressing symptoms that require treatment. These symptoms may be due to the disease itself or secondary to their treatment. Common symptoms include nausea, pain, loss of appetite, constipation and abdominal distension. This is too small a space to describe all the possible treatment strategies involved but it is worth emphasizing a few principles. It is important to take a history, examine the patient and review the drug chart and casenotes. Then consider what investigations may be helpful and what drug or intervention will best treat the most likely cause of her symptoms. These patients are usually complex with multiple problems, however, a logical and systematic approach will help to identify the best treatment. Subcutaneous infusions delivered by
syringe driver are useful as they permit a steady concentration of drug and oral medications may be poorly absorbed. Several hospices publish their guidelines for managing symptoms in palliative care on the internet, which can be very helpful.

Finally, the physical needs of a seriously ill patient are only one facet of their care. Social, spiritual and emotional needs also need to be addressed, both for the patient and their relatives. Specialist oncology nurses and palliative care input is essential, as are discussions on resuscitation status and preferred place of death. These aspects of care are easily overlooked but can make the difference between a peaceful and a difficult death.

**FURTHER READING**


NICE clinical guideline 122, Ovarian Cancer.


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**Practice points**

- Ovarian cancer is best managed within a cancer centre by a multidisciplinary team.
- Women with symptoms suggestive of ovarian cancer should have a CA 125 performed as an initial screen, followed by ultrasound if abnormal.
- Ovarian cancer screening with ultrasound and CA 125 does not appear to helpful in the low risk population.
- Treatment involves a combination of surgery and platinum-based chemotherapy.
- Fertility sparing surgery is possible in women with early stage disease.