Ovarian cancer

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Epithelial ovarian cancer is the commonest cause of gynaecological cancer-associated death. The disease typically presents in postmenopausal women, with a few months of abdominal pain and distension. Most women have advanced disease (International Federation of Gynecology and Obstetrics [FIGO] stage III), for which the standard of care remains surgery and platinum-based cytotoxic chemotherapy. Although this treatment can be curative for most patients with early stage disease, most women with advanced disease will develop many episodes of recurrent disease with progressively shorter disease-free intervals. These episodes culminate in chemoresistance and ultimately bowel obstruction, the most frequent cause of death. For women whose disease continues to respond to platinum-based drugs, the disease can often be controlled for 5 years or more. Targeted treatments such as antiangiogenic drugs or poly (ADP-ribose) polymerase inhibitors offer potential for improved survival. The efficacy of screening, designed to detect the disease at an earlier and curable stage remains unproven, with key results expected in 2015.

Introduction

Epithelial ovarian cancer is the fourth commonest cause of female cancer death in the developed world. The reason for the high death rate is the late presentation in most cases, meaning that the disease is widely metastatic within the abdomen. Although with modern management, a significant proportion of women attain complete response, most of those who present with advanced disease will develop recurrence within 18 months. For some patients, the tumour remains sensitive to periodic retreatment with platinum-based chemotherapy, becoming relatively chronic and free of debilitating symptoms until chemoresistance restricts further treatment options.

The management of epithelial ovarian cancer needs expertise in surgery, chemotherapy, imaging, histopathology, and palliation; specialist multidisciplinary teamwork is essential to achieve optimum outcomes. The histopathology of epithelial ovarian tumours is heterogeneous and each epithelial ovarian cancer subtype harbours genetic mutations that are being assessed for their potential to predict the efficacy of molecularly targeted treatments. With an overall survival at diagnosis of roughly 40% and the continuing development of new treatments, the medium-term outlook for women with ovarian cancer is far better than it was.

This Seminar focuses on epithelial ovarian cancer rather than the much rarer germ cell, sex cord, or stromal tumours. We describe clinical management and the emerging role of targeted treatment based on knowledge of the molecular pathology and consideration of the prospects for effective screening.

Search strategy and selection criteria

We searched the Cochrane Library and PubMed for relevant randomised trials and other high-quality studies (eg, systematic reviews and meta-analyses) published in English between Jan 1, 2000, and Sept 1, 2013, with the terms "ovarian cancer", "chemotherapy", "surgery", "VEGF", "BRCA", and "genetics". We also included widely cited older publications that we judged to have important references. We also searched references from relevant articles identified by our search strategy.

Epidemiology and genetics

Every year 220 000 women develop epithelial ovarian cancer worldwide.[1] In the UK, 7000 women develop the cancer (of whom 4200 die every year);[2] in the USA, 22 500 women develop the disease (of whom 14 000 die every year).[3] The age-standardised incidence of the disease[4] has been estimated at 9·4 per 100 000 population in more developed areas, and five per 100 000 population elsewhere.[5] In the UK the lifetime risk of developing ovarian cancer is about one in 60. The median age of patients enrolled in most randomised trials is 58 years; several years younger than the median age of diagnosis (63 years) in the overall population. Women with a genetic predisposition to ovarian cancer are diagnosed roughly 10 years earlier than the median age of diagnosis.[6]

Findings of epidemiological studies have shown that the risk of ovarian cancer is reduced by states of anovulation, such as pregnancy or the use of oral contraception;[7] or through tubal ligation-reduced reflux of menstrual products onto the ovary.[8] Supraphysiological ovarian stimulation for treating infertility has been implicated, but not proven, to increase the risk of borderline ovarian tumours.[9]

In view of the widespread use of oral contraception by the post-war generation, the incidence of ovarian cancer might be expected to be lower in women aged 50–70 years. Some evidence for this has been reported in women aged 50–64 and 40–49 years, in which there has been a decreasing trend between 1993 and 2008.[3] Endometriosis[10,11] and polycystic ovaries[12] have been linked with ovarian cancer. Endometriosis is sometimes found adjacent to endometrioid or clear cell ovarian cancers, and findings of some prospective case-control studies have shown an increased incidence of ovarian cancer in women with documented endometriosis.[13] Human papilloma virus,[14] perineal talc,[15] and smoking[16] have been discounted as causes of the disease, whereas findings of epidemiological and genetic analyses have shown that epithelial ovarian cancer is a major element

in several germline genetic mutation syndromes. The mechanisms of how these genes contribute have not been elucidated. The most common are associated with defective homologous recombination DNA repair, such as the *BRCA1* and *BRCA2* genes,[17,18] or hereditary non-polyposis coli and Lynch syndrome (associated with endometrial and colorectal cancers),[19] where the genes are implicated in base mismatch repair. The five times increased prevalence of particular *BRCA* gene mutations in Ashkenazi Jews compared with the general population places this group at increased risk of ovarian and breast cancer.[20] Additional genetic syndromes include Peutz-Jegher and other rarer disorders.[21]

Histopathology and molecular pathology

Histological interpretation of resected tissue can be complex and needs specialist input. Figure 1 shows the major epithelial ovarian cancer histotypes. The notion of ovarian cancer description and diagnosis is changing, from one disease with several epithelial subtypes to several distinct diseases[22–24] (figure 2). Almost 10 years ago, a new classification was proposed that separated ovarian cancers into type I and II tumours.[26] Type I tumours were low grade; some (endometrioid, mucinous, and clear cell types) harboured mutations in *BRAF*, *KRAS*, and *PTEN* with microsatellite instability. Type II tumours included high-grade serous and carcinosarcoma, which frequently contain mutations in *p53*,[25] *BRCA1*, and *BRCA2*. Integrated genomic analysis of ovarian cancer in several hundred tumours, further delineated four transcriptional subtypes, and identified somatic mutations in *NF1*, *BRCA1*, *BRCA2*, and *CDK12*.[26] Importantly, homologous recombination repair of DNA damage is defective in roughly 50% of high grade serous cancer and NOTCH and FOXM1 signalling are implicated in the pathophysiology of serous tumours (figure 3).[27] Now that prevalent type-associated underlying genetic signatures have been identified, the foundations have been laid upon which personalised medicine should be built over the next decade.

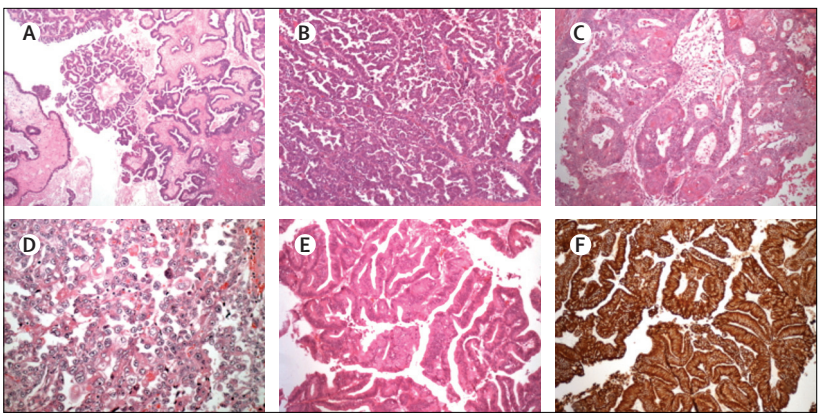

Figure 1: **Examples of different ovarian cancer histotypes**
(A) Borderline tumour: serous epithelium with progressive branching architectural complexity. Some tufting and budding (epithelial cells becoming detached). No high-grade atypia or stromal invasion. (B) High-grade serous tumour: serous epithelium with increased architectural complexity, becoming solid. Glands are elongated with narrow cleft-like spaces showing foci of necrosis and exfoliation. The nuclei are uniformly high grade. (C) Grade 2 endometrioid carcinoma: foci of squamous metaplasia, not seen in (pure) variants of other ovarian carcinomas, are evident. The glands are crowded and fused but the glycocalyx is smooth and the epithelium is generally non-exfoliative. The nuclei are stratified and occupy the full thickness of the epithelium. (D) Clear cell carcinoma of the ovary: uniform high-grade nuclear features with clear cytoplasm; solid and papillary areas are visible with some hobnailing and tufting. The carcinoma is invasive. (E) Well differentiated mucinous carcinoma (H and E) showing progressive archtectural complexity and nuclear atypia. The epithelium towards the benign end of the spectrum shows tall columnar cells with basal nuclei. Areas of definite stromal invasion are difficult to identify but when tumours are this complex, histopathologists prefer a diagnosis of well differentiated carcinoma. (F) Mucinous carcinoma: cytokeratin 7 (CK7)—diffuse staining of tumour cells. CK7 staining in conjunction with patchy CK20 and CDX-2 (CK20 and CDX-2 not shown) are consistent with a primary tumour of ovarian origin.

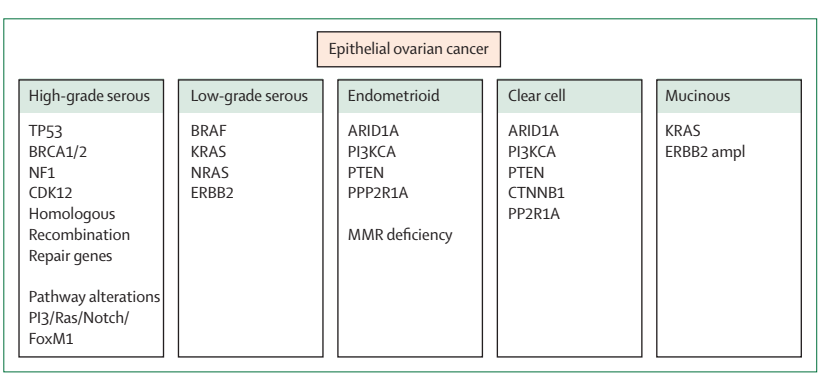

Figure 2: **Epithelial subtypes and associated mutations**
Adapted from Banerjee and colleagues[25] by permission of AACR.

High-grade serous and endometrioid ovarian cancers

Most patients with epithelial ovarian cancer have high-grade serous cancer, a disease that is characterised by nearly universal *p53* gene abnormalities,[28,29] also seen in endometrioid and other high-grade undifferentiated histologies. Although these tumours were believed to have developed from the ovarian surface epithelium, the implementation of prophylactic salpingo-oophorectomy for familial risk has shown a high prevalence of tubal carcinoma or precursor serous tubal intraepithelial carcinoma in resected tissue, resulting in the hypothesis that the tubal fimbriae might be the site of origin of most high-grade serous cancer.[30,31]

High-grade serous cancer is characterised by genomic instability, DNA copy number abnormalities, but few distinct and recurrent mutations.[27] Nearly all ovarian cancers related to deleterious mutations in *BRCA1* and *BRCA2* are high-grade serous cancer. Genomic studies have subdivided high-grade tumours into four subgroups termed proliferative, immunologic, mesenchymal, and differentiated.[27,32] However, this classification has not yet been applied to clinical care. High-grade cancers are characterised by initial chemosensitivity with subsequent acquisition of increasing resistance at each recurrence.

Low-grade serous and endometrioid ovarian cancer

Low-grade serous ovarian cancer shows more indolent behaviour and retrospective studies describe low

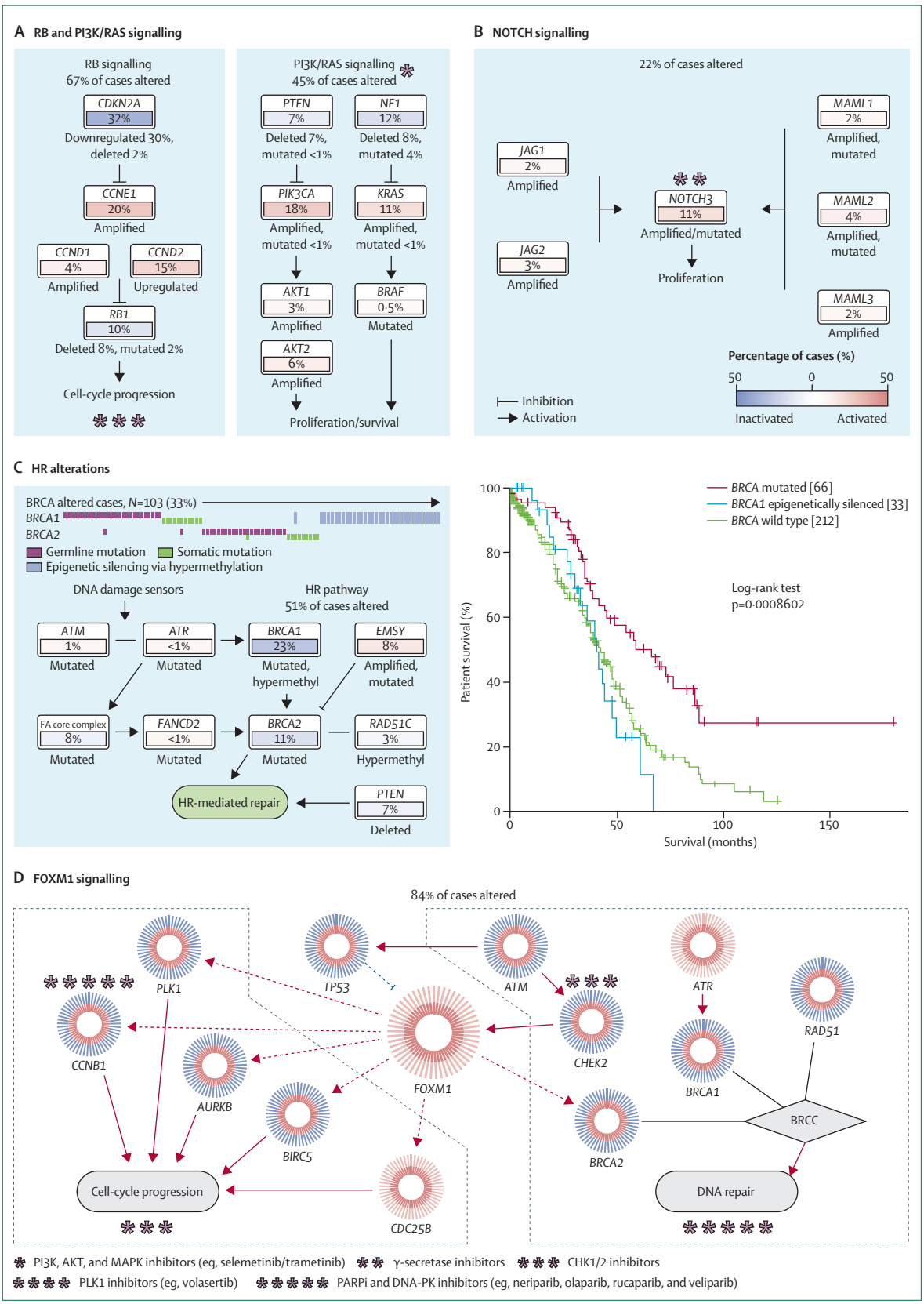

Figure 3: **Altered pathways in high-grade serous ovarian cancer**

(A) RB and (B) PI3K/RAS pathways identified by curated analysis (A), and the NOTCH pathway identified by HOTNET analysis (B). Changes are defined by somatic mutations, DNA copy number changes, or sometimes by substantial upregulation or downregulation relative to expression in diploid tumours. Alteration frequencies are expressed as a percentage of all cases; activated genes are red and inactivated genes are blue. (C) Genes in the homologous recombination pathway are changed in up to 51% of cases. Survival analysis of *BRCA1* and *BRCA2* status shows a divergent outcome for cases with mutations in *BRCA1* and *BRCA2* (with higher overall survival) compared with *BRCA1* and *BRCA2* wild type, and that BRCA1 epigenetically silenced cases have poorer outcomes. (D) FOXM1 transcription factor network is activated in 84% of cases. Each gene is depicted as a multi-ring circle in which its copy number (outer ring) and gene expression (inner ring) are plotted such that each spoke in the ring represents one patient sample, with samples sorted in increasing order of FOXM1 expression. Excitatory interactions (red arrows) and inhibitory interactions (blue lines) were taken from the US National Cancer Institute Pathway Interaction Database. Dashed lines show transcriptional regulation. Asterisks denote potential molecular targets of novel agents. FA=Fanconi anaemia. Reproduced from Bell and colleagues,[27] by permission of Nature Publishing Group.

response rates to cytotoxic and hormonal agents. Mutations in *PI3KCA*, *BRAF*, and *KRAS*, are prevalent and although MEK inhibitors seem promising, these mutations are often absent in responders.[33] As a result, no predictive biomarkers exist to guide treatment.

Clear-cell ovarian cancer

Clear-cell and low-grade endometrioid epithelial ovarian cancer bear frequent mutations in the *ARID1A* gene[11] and might be associated with endometriosis. Clear cell cancers respond poorly to chemotherapy and clinical trials are being developed for this type of ovarian cancer to take advantage of its kinase-inducing pseudohypoxic drive,[34] and the *PIK3CA* gene mutations found in a third of cases.

Mucinous ovarian cancers

Mucinous ovarian cancers are most commonly diagnosed at an early stage. The incidence of true advanced ovarian mucinous tumours has reduced through the application of immunohistochemistry for the cytokeratins CK7 and CK20, which help histopathologists to distinguish ovarian from the more common gastrointestinal source of these cancers (figure 1). This rare type of cancer has nearly 100% *KRAS* mutation and a high frequency of HER2 amplification. Overall, the availability of high quality immunohistochemistry with specialist histopathology coupled with tissue or germline mutational analysis defines distinct types of ovarian cancer that now affect clinical management.

Presentation

Ovarian cancer typically presents with 3–4 months of abdominal pain or distension,[35] which might be mistakenly attributed to irritable bowel syndrome.[36] The UK National Institute for Health and Clinical Excellence (NICE) has recommended that patients who develop symptoms like irritable bowel syndrome, especially those older than 50 years, should undergo measurement of serum cancer antigen 125 (CA-125) concentrations as a secondary screen.[37] If symptoms persist in the absence of raised CA-125 concentration, a low threshold should be set to proceed to pelvic ultrasound.

Primary disease

Women with germline *BRCA1* or *BRCA2* mutations have a 40–60% lifetime risk of epithelial ovarian cancer.[6,38] For women in whom fertility is no longer an issue, risk-reducing salpingo-oophorectomy is the most protective strategy.[39] Younger women can opt for annual screening by pelvic ultrasound, though this has not been shown to reduce the risk of developing epithelial ovarian cancer.

Ovarian cancer typically presents to general practitioners or gynaecologists, but because of the diverse symptoms in late-stage disease, women can present to various medical specialists. Measurement of serum CA-125 concentration and abdominal and transvaginal ultrasound[38] are the key investigations when ovarian cancer is suspected. A risk of malignancy index (RMI; panel 1)[40] is often used in the UK to establish the

Panel 1: Risk of malignancy score

The risk of an ovarian cyst being malignant needs to be estimated because cysts thought to be benign can be operated on by a general gynaecologist and a unilateral oophorectomy can be planned for. If a cyst is believed to carry a substantial risk of being malignant, then the woman needs to be counselled and operated on by a gynaecological oncologist. The conventional means of assessing this risk is the risk of malignancy index (RMI).[40] The RMI is calculated from the ultrasonic features of the cyst, the menopausal status, and the cancer antigen 125 (CA-125) concentration in the blood. Cyst complexity and the menopausal status are scored as below, multiplied together and the product is then multiplied by the CA-125 concentration. A cyst with multilocular, solid components, ascites, or suspected metastases each score 1 to a maximum of 3. Premenopausal status scores 1 and postmenopausal status scores 3. For example a cyst with solid areas and multiloculated, in a postmenopausal woman with a CA-125 of 90 would score 3×3×90=810. An RMI exceeding 200 is judged as a significant risk of malignancy.

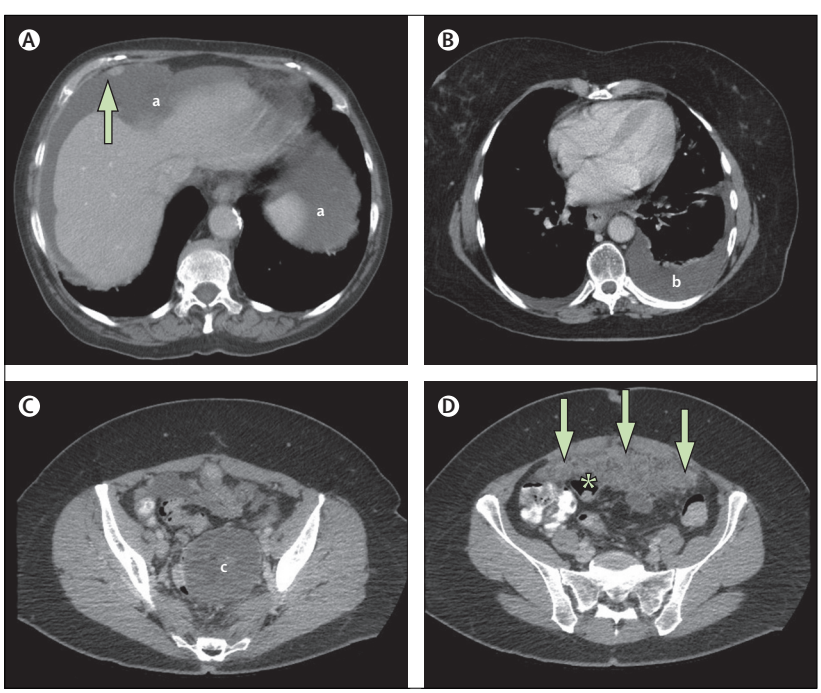

Figure 4: **Common CT findings in advanced ovarian cancer**
(A) 72-year-old with high-grade serous adenocarcinoma stage IV. Moderate volume ascites (a) surrounds the liver and spleen. Arrow shows a peritoneal nodule. (B) 61-year-old with high-grade serous adenocarcinoma stage IIIc. Small volume left-sided pleural effusion (b). A trace of pleural fluid is also present in the right hemithorax. (C) and (D) 76-year-old with poorly differentiated serous adenocarcinoma stage IIIc. Bilateral adnexal masses were present. A mixed cystic and solid left adnexal mass (c) is shown, occupying a central location in the pelvis. Large volume infracolic omental cake present (arrows), which invades the serosa of the transverse colon (asterisk).

Panel 2: **International Federation of Gynecology and Obstetrics staging of ovarian cancer**

I Disease limited to ovaries only
- **Ia** Limited to one ovary only
- **Ib** Both ovaries affected
- **Ic** Ia or Ib with tumour on the surface of one or both ovaries, ruptured capsule, cytologically positive ascites, or positive peritoneal washings

II Disease extending to the pelvis
- **IIa** Disease affecting tubes or uterus or both
- **IIb** Extension to other pelvic tissues
- **IIc** IIa or IIb with tumour on the surface of one or both ovaries, ruptured capsule, cytologically positive ascites, or positive peritoneal washings

III Abdominal disease or affected lymph nodes or both (surface liver disease is still stage III)
- **IIIa** Microscopic involvement of abdominal peritoneal surfaces.
- **IIIb** Disease up to 2 cm diameter
- **IIIc** Disease greater than 2 cm +/– regional lymph nodes

IV Distant metastases: pleural effusions need to be cytologically positive and liver metastases should be parenchymal

The FIGO staging system was recently updated[41]

likelihood that a complex (solid/cystic) mass is malignant, and to triage referral from generalists to specialist gynaecological oncologists. The exact RMI threshold for direction of management remains a topic of research.

Unfortunately the non-specific presentation to general practice or non-gynaecological specialists can result in a vaginal examination not being done, which could show an obvious pelvic mass that might be associated with abdominal swelling and gross ascites. Abdominopelvic CT scanning can be used to estimate the extent and sites of tumour involvement (figure 4). MR scanning might be helpful in further assessment of the pelvic tumour. Sometimes the tumour arises in the peritoneum producing widespread low volume cancer, without a discrete ovarian tumour, in which case the tumour is referred to as a primary peritoneal cancer, which is almost always of serous type.

Surgery

The purpose of surgery is to provide a histopathological diagnosis, to remove as much cancer tissue as possible, and to establish the FIGO stage, which has recently been updated[41] (panel 2). Surgery should include a total hysterectomy, bilateral salpingo-oophorectomy, tumour debulking, and omentectomy.[38] Surgery should be done by a gynaecological oncology surgeon.[42–44] Lymphadenectomy is necessary in FIGO staging, but findings of trials have not shown that extensive retroperitoneal lymphadenectomy confers a survival advantage.[45] The clinical effectiveness of lymphadenectomy, other than for comprehensive staging of early disease, is unproven and is being assessed in a German randomised trial (LION ISRCTN05335540). However, staging might prevent the need for adjuvant chemotherapy in stage I disease in which nodes are unaffected, or conversely it might identify occult (stage III) disease in up to 30% of patients.[46]

Recently, there has been a trend towards greater surgical intent with respect to optimum debulking including multidisciplinary surgical teams. Consideration of whether optimum surgical debulking is feasible should include fitness for surgery, and imaging might be helpful. Adverse factors that might reduce the chances of successful complete primary debulking surgery include extensive upper abdominal disease, involvement of the porta hepatis, small bowel mesentery and diaphragm, extensive ascites, or spread beyond the abdominal cavity (FIGO stage IV disease).[47] In some centres, direct visual inspection by laparoscopy is used to establish operability to avoid fruitless laparotomy. When the patient's condition is poor, pre-operative chemotherapy is used after histological confirmation of the disease by percutaneous biopsy.

Data from retrospective studies[48] suggest that minimum residual disease after surgery is associated with longer survival, but whether this association is causal or whether resectable tumours are intrinsically biologically more chemosensitive and less aggressive is unclear. A trial addressing this issue would include randomly assigning patients to standard or aggressive surgical effort to debulk and would be ethically and methodologically difficult. Nonetheless, with improved perioperative support and multidisciplinary surgical teamwork, there is greater focus on trying to achieve total debulking within the bounds of acceptable morbidity and perioperative mortality.

The strategy of using neoadjuvant (preoperative) chemotherapy when complete surgical debulking is not deemed feasible at diagnosis is widely accepted. Interval debulking surgery is done during the chemotherapy course typically after three of the six cycles. This approach is supported by a large randomised trial,[49] which reported non-inferior survival and a reduction in postoperative morbidity. A second trial (CHORUS)[50] has been reported as a conference abstract and reached a similar conclusion. No evidence that a second surgical procedure to complete tumour debulking after chemotherapy improves survival exists, and this cannot be recommended.[51]

In fertile women with unilateral stage I disease, conservative surgery should be considered. In these patients, borderline ovarian tumours (tumours of low malignant potential) are more common and are adequately managed by a more conservative approach, thereby preserving fertility. However, such cases do need careful surgical staging to look for occult disease. A well differentiated unruptured stage Ia ovarian cancer can be

managed without removal of the contralateral ovary if it looks normal, thus maintaining fertility if desired. Preoperative discussion is crucial to ensure that the patient is aware of the different therapeutic options. Women with unilateral high-grade disease might be offered post-operative adjuvant chemotherapy, which generally does not affect subsequent fertility if the uterus and other ovary are functioning normally and are disease free.

Cytotoxic chemotherapy

First-line chemotherapy for early stage disease

Adjuvant chemotherapy in early stage disease, which comprises about 20% of epithelial ovarian cancer, improves overall survival by 8% incurring a hazard ratio in favour of treatment of 0·67.[49,50] Data from these two adjuvant trials suggest there might be no benefit from adjuvant chemotherapy in patients who have undergone complete debulking and staging surgery.[52] However, results from long-term follow up of patients with stage I disease in ICON1 showed that treatment with cytotoxic chemotherapy should be considered in patients with: grade 3 or clear cell; grade 2/3, stage Ib; and grade 1–3 stage 1c disease.[53]

First-line chemotherapy for advanced disease

Regimens containing platinum have been the standard of care for almost 40 years worldwide, although recent findings have started to affect the options for first-line treatment (table). In one study,[61] survival was improved when paclitaxel was added to cisplatin, as a result, six three-weekly cycles of the less toxic carboplatin is now given in combination with a paclitaxel or docetaxel.[62,63] Attempts to improve the efficacy by adding a third cytotoxic agent were not successful.[64] Thus, the global standard of care for the past 20 years has remained carboplatin and paclitaxel. Although response to this treatment is traditionally followed radiologically, the serum CA-125 concentration is also useful.[65–67]

Findings of five positive randomised trials[55–57,68,69] have started to affect the options for first-line treatment (table). In two trials,[56,57] the antiangiogenic antivascular endothelial growth factor (VEGF) antibody bevacizumab was incorporated, and in a third, pazopanib, a VEGF receptor tyrosine kinase inhibitor (VEGF RTKi) was used as maintenance treatment.[68] A different approach was taken in a Japanese study (JGOG 3016),[55,69] which showed that fractionating paclitaxel into a dose-dense weekly schedule improved the progression-free survival (PFS) and overall survival (OS). This difference in survival was impressive and led to the establishment of two further trials (National Cancer Research Network [NCRN] ICON8 trial [ISRCTN10356387] and GOG262 [NCT0116771]) in non-Japanese populations to see if the value of this approach can be confirmed.

The fifth trial that raised interest and much debate was a randomised trial of intraperitoneal chemotherapy.[54] Here intraperitoneal and intravenous chemotherapy with cisplatin and paclitaxel were compared with intravenous cisplatin with paclitaxel. The experimental group, incorporating higher dose of cisplatin and dose-dense paclitaxel, showed significantly improved survival but was only deliverable in 42% of patients, largely because of neurological and gastrointestinal toxic effects. Despite enthusiasm for the approach and its potential to deliver cytotoxic chemotherapy to the tumour in markedly greater concentrations than those achievable by intravenous delivery, general uptake has been poor and more tolerable intraperitoneal regimens are being assessed in trials.

	Findings
Armstrong,2006[54]	Intraperitoneal chemotherapy improves PFS and OS but is toxic
Katsumata, (JGOG) 2009[55]	Dose dense paclitaxel improves PFS and OS incurred from first line therapy in Japanese patients; confirmatory trials in USA and Europe are in progress
Burger, 2011,[56] and Perren, 2011[57]	Anti-VEGF antibody-containing regimens improve PFS in the first-line treatment setting
Aghajanian, 2012,[58] and Pujade-Lauraine, 2012[59]	Anti-VEGF antibody-containing regimens improve PFS in the platinum sensitive and resistant setting
Ledermann, 2012[60]	PARP inhibitors improve PFS in high-grade serous ovarian cancer

PFS=progression-free survival. OS=overall survival. PARP=poly (ADP-ribose) polymerase.

Table: **Key recent positive phase 3 clinical trials**

Recurrent disease

Recurrence can be detected in several ways. The earliest indication of recurrent disease might be a doubling in CA-125 concentration[70] above the upper limit of normal, with neither radiological nor clinical evidence of disease. Although not routinely used in follow up, a CT scan can detect an asymptomatic recurrence or relapse might present with symptoms and a clinically detectable mass. Further treatment should be initiated on the basis of the clinical features, radiological findings, and the preferences of the patient and her oncologist.

Most patients with recurrent disease receive second-line chemotherapy, but a subset can be considered for second surgery. This subset is characterised by a discrete tumour mass for which the prospect of resection is good; absence of gross ascites; fitness for surgery; and complete resection at initial surgery;[71] these data have led to prospective randomised trials of surgery in recurrent disease (NCT01166737 and NCT00565851). Otherwise, surgery is only occasionally done—eg, to palliate intestinal obstruction caused by an isolated site of disease.

In an important trial[72] of the timing of second-line chemotherapy, women who developed recurrent disease were randomised to receive chemotherapy on the basis of either recurrence detected by CA-125 concentration, which typically happens 3–4 months before clinical presentation, or on clinical relapse. Early intervention because of a rising CA-125 concentration did not improve survival and these patients had a worse quality of life because of earlier treatment with chemotherapy in a period when they would otherwise have been asymptomatic. The choice of

chemotherapy regimen for recurrent ovarian cancer is dictated to a large extent by the interval from the last cycle of platinum-containing treatment to the point of disease progression.[73,74] Platinum-resistant disease has been defined by retrospective studies as progression within 6 months of the last platinum-containing regimen, with a less than 15% potential for response to re-treatment with platinum. Patients with a platinum-free interval of 6 to 12 months have partly platinum-sensitive disease, with increasing sensitivity for those whose recurrence occurs after 12 months.[74,75]

The median PFS of advanced ovarian cancer is about 18 months. Because first-line chemotherapy regimens last roughly 4·5 months, most recurrent disease is platinum sensitive. Findings of randomised trials have shown that platinum-sensitive recurrent disease is best treated with a combination of platinum-containing drugs such as carboplatin with paclitaxel, gemcitabine,[76–78] or pegylated liposomal doxorubicin.[79] Typically, the strategy of using platinum-containing regimens continues while the patient has platinum-sensitive disease until eventually the patients develop platinum-resistant disease.

Patients with the worst prognosis are those whose disease progresses on platinum-containing treatment (platinum refractory) or those with platinum-resistant disease. Historically such women have been managed with one drug, such as pegylated liposomal doxorubicin or topotecan,[80] which produce low response rates. However, some patients benefit from dose-dense regimens, which are more active than one drug.[81–83] This group is also well served by entering trials of new agents and regimens. Chemosensitivity assays or genetic screening arrays that establish drug sensitivity have been studied, but remain unproven.[84,85]

New treatment strategies

BRCA gene mutations, BRCAness, and poly (ADP-ribose) polymerase inhibitors

About 15% of (mostly serous) ovarian cancers are associated with germline mutations of the *BRCA1* or *BRCA2* genes and up to 25% of unselected high-grade serous cancers harbour mutations in *BRCA1* or *BRCA2*. The BRCA genes are needed for normal repair of double-stranded DNA damage through homologous recombination. Recent evidence has shown that homologous recombination deficiency might occur in up to 50% of sporadic high-grade serous cancers due to germline or somatic *BRCA* gene mutation, epigenetic silencing, or other mutations that affect homologous recombination competency.[27,86] Patients with germline *BRCA* mutations often have tumours that show increased chemosensitivity to platinum (and other DNA damaging agents), corresponding with a longer survival than in women with sporadic ovarian cancer.[87] In addition to family history, which often fails to predict for mutations,[88] visceral involvement and prolonged sensitivity to platinum agents are recognised indicators for the presence of *BRCA* mutations.[89]

The mechanism underlying this chemosensitivity is related to the crucial role BRCA proteins have in homologous recombination. In patients with homologous recombination deficiency, there is increased reliance on the poly (ADP-ribose) polymerase (PARP) single-strand repair pathway such that PARP inhibitors cause significant tumour lethality, because cells are unable to repair spontaneous DNA damage. Impressive tumour responses and clinical benefit have been seen with olaparib, a PARP inhibitor, in phase 1 trials[90] and in randomised trials comparing the drug with liposomal doxorubicin.[91]

Studies of PARP inhibitors have been broadened to include patients with sporadic high-grade serous cancer and germline *BRCA*-mutated recurrent tumours. Maintenance olaparib given to patients with recurrent disease, after a further response to platinum-based treatment, led to a significant improvement in PFS, with few toxic effects after prolonged administration.[60] However, differences in survival have not yet been shown, possibly because many patients receive several subsequent lines of treatment, including PARP inhibitors.[92] These studies have paved the way for further trials with PARP inhibitors in patients, mostly as maintenance therapy alone, since combination with cytotoxic chemotherapy can lead to additive myelotoxicity. Identification of a predictive biomarker, other than *BRCA* mutation, is critical for the selection of patients who are most likely to benefit from these agents.

Antiangiogenic treatment and effective maintenance treatment

Tumours need new blood vessels to grow and to spread through vascular metastasis. Inhibition of angiogenesis, restrains tumour growth and the main, prototypic target of antiangiogenic treatment in the clinic is VEGF. The cytokine has been inhibited predominantly through anti-VEGF antibodies and low molecular weight VEGF RTKi, although soluble dominant negative receptor constructs are also entering the clinic.[93]

Most clinical experience in ovarian cancer has included the monoclonal anti-VEGF antibody, bevacizumab. Seven randomised trials have validated angiogenesis as a target in ovarian cancer through the addition of VEGF pathway inhibitors to conventional therapeutic regimens. Results of two first-line trials (GOG218[56] and ICON7[57]) have shown that patients with FIGO stage III/IV disease with any residual tumour after primary surgery benefit from the addition of bevacizumab to carboplatin and paclitaxel chemotherapy followed by maintenance treatment. Data from the oral VEGF RTKi maintenance trial with pazopanib[68] are now available and firmly support the activity of antiangiogenic treatment in ovarian cancer. Further positive trials with the VEGF RTKis, cediranib and nintedanib, have also been reported recently.[94]

Data from these first-line trials represent a large advance in the treatment of ovarian cancer. Although cytotoxic chemotherapy induces high response and disease control rates, previous attempts to consolidate[95] or maintain[96,97] the benefit of treatment with further cytotoxic drugs failed to improve survival. Clearly, antiangiogenic drugs improve PFS through effective maintenance treatment. However, only two trials, ICON6 and ICON7, have reported overall survival benefits.

Two further trials in platinum-sensitive[58] and platinum-resistant[59] tumours have shown that the addition of bevacizumab to cytotoxic treatment improves PFS. Improvement in OS was not seen in the platinum-sensitive disease group probably because of crossover and many lines of post-progression treatment. The final results of the platinum-resistant trial have not been published and therefore the optimum positioning of VEGF inhibitors in ovarian cancer is not yet defined. Interpretation of the value of a gain in PFS without an OS advantage is complex but important because experimental[98] and clinical data suggest antiangiogenic agents seem to provide continuous benefit.[98] If a patient only gains a PFS advantage, her quality of life might be slightly impaired[99,100] by the continued need for long-term prescription. Furthermore, to show an acceptable level of cost-effectiveness of such expensive drugs is difficult without survival gain and biomarkers that can select those most likely to benefit. These drugs are associated with hypertension and proteinuria but more importantly, in patients with extensive pretreatment, pelvic disease or bowel obstructive symptoms, they might also cause bowel perforation[101] or fistula formation. Thus, the continual risk to the patient needs to be balanced against the known benefits from these drugs.

Other antiangiogenic drugs target other pathways, such as the Angiopoietin/Tie2[102] and these are in late-stage clinical trials. As more antivascular agents enter the clinic, predictive biomarkers will be crucial so that efficacy and cost can be optimised and toxic effects can be minimised.

New drugs

Molecularly targeted treatment has emerged consequent to our improved understanding of the underlying biology of ovarian cancer. Despite some negative trials (eg, with the anti-CA-125 antibody oregovomab),[103] further targeted trials have capitalised on the widespread overexpression of the folate receptor-α[104] or have generated more complex therapeutics where a cytotoxic drug is conjugated (vintafolide[105]) to deliver high concentrations of cytotoxic agent to tumours expressing high levels of the folate receptor.[106] Large-scale randomised trials are now in progress. Alternative immune strategies are of interest but have not yet translated into clinical benefit.

Our knowledge about genetic mutations in ovarian cancer is leading to the assessment of mutation-focused, mechanism-based treatment. Figure 2 shows the major gene mutations and their associated epithelial phenotypes and the association between relevant gene mutations and the activity of suitably targeted drugs is of significant interest. The convergence of the PI3K/AKT signalling pathway on mTOR and their importance in ovarian cancer[107] have led to the assessment of inhibitors of both signalling components. Published data with mTOR inhibitors have not been encouraging[108] and are associated with the class-specific effects of hyperglycaemia and hyperlipidaemia.[109] Several PI3 kinase inhibitors[110,111] are also in early clinical development. However, these inhibitors are also associated with class-related diarrhoea and other toxic effects making these drugs difficult to develop. MEK/ERK mitogen-activated proliferation kinase (MAPK), which is commonly activated in ovarian cancer, is downstream of PI3K/AKT and RAS/RAF and other major pathways. Selemetinib, a selective MAPK inhibitor, was examined for activity in recurrent low-grade serous ovarian cancer,[33] yielding a median PFS of 11 months. However, no association was reported between KRAS, BRAF, or RAS protein mutations and outcome.

In addition to gene mutation-targeted therapeutics, angiogenesis and cell proliferation share many common ligands, which should be targeted. These include the FGFs,[112] PDGFs,[112] and HGF/c-Met.[113] Several agents that target these molecules are in the clinic and are likely to have some activity; the major problem in their development is the elucidation of predictive biomarkers.

Endocrine treatment, hormone replacement therapy, and bone density

Historically, the oestrogen receptor has been detected in roughly 60% of ovarian cancer samples, but the disease is not responsive to oestrogen and only occasionally responsive to endocrine agents such as tamoxifen[114] or letrozole.[115,116] These drugs might be more useful in low-grade disease where cytotoxic agents yield a low response rate.[117] While expression of oestrogen receptor is not predictive of efficacy to the degree seen in breast cancer, some centres identify oestrogen receptor expression to help with decision making.

A second important issue in ovarian cancer concerns the use of hormone replacement therapy. Generally, hormone replacement therapy is safe and appropriate[118,119] in patients younger than 50 years, especially because these patients would otherwise have been exposed to oestrogen until their menopause. The potential quality of life benefit from hormone replacement therapy needs to be balanced against its risks, though in the absence of a uterus, oestrogen only hormone replacement therapy can be considered safe. In patients younger than 50 years who undergo bilateral oophorectomy and where long-term survival is predicted, measurements of bone density every 2–3 years and institution of appropriate treatment if needed are appropriate.

Panel 3: **Useful websites for patients**

- Cancer Research UK: http://www.cancerresearchuk.org/cancer-help/type/ovarian-cancer/
- MacMillan Cancer Support: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Ovary/Ovariancancer.aspx
- US PDQ: http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/Patient
- US National Comprehensive Cancer Network: http://www.nccn.org/patients/patient_guidelines/ovarian/index.html

Prognosis

The prognosis of ovarian cancer is associated with performance status, FIGO stage, and the volume of residual disease after initial debulking surgery. Recent data have suggested that thrombocytosis is associated with advanced stage and shortened survival.[120] Survival from the disease varies between and within countries. Although survival figures are potentially confounded by the quality of data collected, in the UK, 5 year survival seems to have steadily improved,[121] which is most likely due to the implementation of specialist services. Nevertheless, the median survival of ovarian cancer when treated in major treatment centres is now roughly 40–50% at 10 years with stage-related survival for stages I, II, III and IV of 73–92%, 45–55%, 21% and <6%, respectively.[2,122]

Additional notable survival statistics include: 50% of patients with FIGO stage III disease, who achieve a pathological complete response after surgery and chemotherapy have more than 5 years survival;[123] recurrent disease is usually incurable but very treatable; the median survival of patients with recurrent platinum-sensitive ovarian cancer is roughly 3 years; the median survival of patients from the time of onset of platinum-resistance is about 1 year.[124] However, many patients have disease that is amenable to treatment with several lines of cytotoxic chemotherapy over many years. Effectively, we are treating some patients for a chronic disease and in these cases, a balance of re-introduction of chemotherapy against quality of life, symptom control, and psychological wellbeing is crucial (panel 3).

Cause of death and symptom palliation

Most patients who succumb to ovarian cancer die from malignant bowel obstruction, which usually affects many parts of the bowel and is therefore not amenable to surgery. Symptom palliation is vital and the treating physician should work in conjunction with specialist palliative care teams to optimise control of nausea, vomiting, colicky abdominal pain, non-colicky pain, and constipation. Dietetic input is also helpful because patients benefit from a low residue diet. Such patients frequently develop ascites that can be drained, and in patients with intractable ascites, indwelling ascitic drains afford patients the opportunity of home-based drainage procedures. Bowel obstruction in ovarian cancer remains a difficult disorder to treat that might pose difficult ethical issues[125] such as the use of total parenteral nutrition in patients whose other organ systems are unaffected by the disease.

Screening

Success in screening for ovarian cancer requires a sufficiently sensitive and specific test to detect curable cancer. Attempts to screen the general population with measurement of serum CA-125 concentration, transvaginal ultrasound, or both have not yet provided convincing evidence that early-stage, curable ovarian cancer can be detected in sufficient numbers, without an excessive number of non-malignant lesions precipitating unnecessary surgery.[126,127] Unlike cervical cancer, ovarian cancer does not have a detectable pre-invasive phase, and little evidence exists for progression from stage I to stage III disease.

The UKCTOCS trial has randomly assigned more than 200 000 women to observation or CA-125 measurement, which if increased, triggered TVUS. The results of the prevalence screen have been published,[128] in terms of stage distribution, and sensitivity and specificity of CA-125 and TVUS. The final results will be available in 2015. Until then, screening of the general population cannot be recommended. Irrespective of the trial results, the UKCTOCS biological sample collection has the potential to identify susceptibility genes[129,130] or other biomarkers that might underpin screening or early detection.

Women at high risk of developing ovarian cancer (eg, those with deleterious germline *BRCA* mutations) in whom the risk of developing ovarian cancer is 55–60%,[6] need different consideration. In the UK Familial Ovarian Cancer Screening Trial (UKFOCCS),[131] frequency of early stage screened cases was 31%; positive predictive value was 25% for a positive screen, with a negative predictive value of 99%. Nevertheless, without survival benefit in these patients, prophylactic surgery remains an established option.[39]

Future perspectives

The efficacy of cytotoxic treatment has been improved by the introduction of dose-dense treatments, and is being assessed in first-line trials. VEGF pathway inhibitors improve the response rate when added to traditional cytotoxic regimens and prolong disease control when given as one drug maintenance treatment. However, VEGF pathway inhibitors are probably not being used optimally. Maintenance treatment almost certainly needs longer treatment, perhaps until or even beyond progression; the question is whether alternative antivascular drugs should be selected beyond progression on VEGF inhibitors. PARP inhibitors are a new class of drug that will broaden the therapeutic options for many patients with high-grade serous cancer.

Their optimum usage will emerge from continuing trials. In the next decade, other new active drugs will emerge. Selection of the most appropriate treatment, on the basis of tumour phenotype and evolving genotype, and use of these drugs at the appropriate phase of disease remains a large challenge.

Declaration of interests
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