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 ultra-radical surgery, intra-peritoneal chemotherapy and novel drug treatments.

Keywords chemotherapy; ovarian cancer; screening; surgery

Introduction

Ovarian cancer has the highest mortality of all the gynaecological malignancies. Epithelial ovarian cancer is the most common subtype. Different types of ovarian cancer vary significantly in their clinical and molecular characteristics. Up to 20% of women with epithelial ovarian cancer have an inherited predisposition. In this group risk reducing surgery can be an option. Routine screening with serum CA 125 and pelvic ultrasonography has no proven value. Diagnosis of ovarian tumours is usually made by pelvic ultrasonography and serum CA 125. The risk of malignancy index is then calculated in order to decide where treatment takes place. Treatment of advanced ovarian cancer usually involves primary debulking surgery and adjuvant chemotherapy but neo-adjuvant chemotherapy with interval debulking surgery is equally effective. Survival is improved if surgery is performed by a specialist gynaecological oncologist. Recent evidence supports the value of radical surgery aiming to excise all macroscopic disease. Standard chemotherapy for epithelial ovarian cancer is carboplatin with paclitaxel. Recently the first of many tested molecular targeted treatments, bevacizumab, has been added to the armoury against ovarian cancer. Treatment of advanced disease may prolong life and palliate symptoms but it is rarely curative. Novel drugs and approaches such as ultra-radical surgery, intra-peritoneal chemotherapy, and surgery for recurrent disease are being assessed.

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Incidence-mortality

The lifetime risk of ovarian cancer (OC) in the developed world is 1—2%, with 75% of cases diagnosed above the age of 55. Five year survival is significantly affected by stage, being more than 90% for stage I and less than 10% for stage IV disease. Approximately two thirds of cases are diagnosed at stage III. The age standardised 5-year survival in the UK is at 42.9%. Despite significant improvement in survival UK still lags behind Australia, Canada, Norway and Sweden.

Prevention

Breastfeeding, the oral contraceptive pill non-steroidal anti-inflammatory drugs and also aspirin appear to protect against the development of OC. On the contrary endometriosis seems to be associated with higher risk of OC. Ovarian stimulation drugs do not appear to affect the risk of other than borderline tumours. Family history of ovarian or breast cancer are strong predictors of BRCA gene mutation. Endometrial, colon, ovarian and other cancers cluster in families with the Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC). Family history suggestive of high risk for development of ovarian cancer should prompt referral to clinical genetics (Table 1). Patient can themselves estimate their risk using web based tools (http://www.macmillan.org.uk/Cancerinformation/Causesriskfactors/Genetics/OPERA.aspx). Both BRCA and Lynch syndrome are inherited in an autosomal dominant pattern. Clinical genetic services quantify the risks and offer genetic testing when risk of mutation is estimated at 10% or higher. Lynch syndrome mutation carriers have a 12% lifetime risk of developing OC when BRCA 2 carriers have 27% and BRCA 1 have between 28 and 44%.

Risk reducing surgery with bilateral salpingo-oophorectomy (BSO) alone or with hysterectomy is recommended for BRCA 1/2 and Lynch syndrome mutation carriers respectively. This is considered after the age of 35 as long as their families are completed. BSO is reducing risk for both ovarian and breast cancer but a small risk of primary peritoneal cancer is still present. The negative effects of surgical menopause should be discussed. Subsequent hormone replacement therapy is not found to increase the breast cancer risk. Annual ovarian and endometrial surveillance is instated for women that do not undergo surgery.

Screening

Current evidence shows that screening for OC fails to decrease mortality but does increase unnecessary surgery rate (PLCO

Family history criteria of high risk for developing OC

≥2 individuals with OC, who are first degree relatives of each other
1 individual with OC AND one with breast cancer <50 years, who are first degree relatives to each other
1 relative with OC AND two with breast cancer diagnosed <60 years, who have first degree relationships
1 known BRCA carrier
1 relative with both breast and ovarian cancer OR one male with breast cancer
≥3 relatives with colon cancer OR two with colon cancer and one with either: stomach, ovarian, endometrial, urinary or small bowel cancer

Table 1

cancer screening trial). Long-term large multicentre trials (UKTOCS: United Kingdom Trial of Ovarian Cancer Screening and UKFOCS: United Kingdom Familial Ovarian Cancer Screening) are expected to clarify the value of screening for low and high risk populations. Despite limitations and potential risks ovarian surveillance is offered to high risk patients.

The best currently available modalities for screening are still these of pelvic ultrasound scan and the tumour marker Ca 125 (carbohydrate antigen 125). Ca 125 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, pelvic inflammatory disease and pregnancy. It is not specific in low levels but high levels are indicative of advanced epithelial ovarian cancer (EOC). Mucinous tumours produce a more modest elevation of Ca 125 while germ cell tumours can secrete α-FP, b-HCG and LDH. These markers should be tested in addition to CA 125 in women under the age of 40 with a suspicious pelvic mass. Inhibin is of some use as a marker for mucinous and granulosa cell tumours. More recently HE4 (Human Epididymis protein 4), has been identified as another biomarker for ovarian cancer that performs similarly with Ca 125.

The ultrasound and CA 125 together are used to calculate the risk of malignancy index (RMI, Table 2). RMI is used to triage women with suspicious adnexal pathology. Recently the risk of ovarian malignancy index (ROMA), which incorporates menopausal status with Ca 125 and HE4 levels without ultrasonography appears to be a promising predictor of EOC.

Types of ovarian cancer (Table 3)

Primary ovarian tumours can be divided according to their embryological cell of origin into three categories; surface epithelium (coelomic epithelium), sex cord stroma (mesenchyma) and germ cells (mesonephric). More than 80% of ovarian cancers are epithelial predominately serous carcinomas. Tumours not specific to the ovaries also occur, such as sarcomas and lymphomas and metastatic tumours from breast, stomach and endometrial primaries are not uncommon.

Epithelial tumours

Approximately 70% of epithelial tumours are high grade while 5% are low grade serous carcinomas.

Endometrioid and clear cell carcinoma's follow with 10% each, while mucinous account for only 3%. Transitional (Brenner), mixed and undifferentiated tumours are very rare.

It is becoming increasingly evident that these tumours develop and behave as distinct entities.

Serous tumours seem to arise from dysplastic epithelium in the distal fallopian tube and molecular evidence suggests that even low and high grade tumours are different entities. High grade serous tumours are strongly associated with p53, BRCA 1 & 2 mutations and homologous recombination deficiency. Most commonly present at advanced stage and tend to be highly chemo-sensitive. Low grade serous tumours are associated with KRAS, BRAF, NRAS, HER2 mutations, usually have a borderline component and tend to follow a more indolent course being less chemo-sensitive.

Endometrioid tumours are commonly low grade and associated with CTNNB1, PTEN gene mutation and Lynch syndrome. They appear to arise from endometriotic cysts, usually present at early stages, can be bilateral and accompanied by synchronous endometrial cancer. These low grade tumours behave like endometrioid endometrial cancers while their high grade counterparts resemble the high grade serous ovarian cancers.

Clear cell tumours are associated with ARID1A, CTNNB1 and PTEN mutations. They commonly arise on the background of

Risk of Malignancy Index (RMI) = U × M × Ca 125

Ultrasound score = 1 if any 1 of:	Ultrasound score = 2 if any 2–5 of:	Ultrasound score = 0	menopausal status
Multilocular cyst	Multilocular cyst	If none of above	Menopausal = 3
Solid areas	Solid areas		Premenopausal = 1
Bilateral lesions	Bilateral lesions		
Ascites	Ascites		
Metastases	Metastases		

Table 2