Ovarian cancer: current management and future directions

Purushothaman Natarajan

Sian E Taylor

John M Kirwan

Abstract

Of all the gynaecological malignancies ovarian cancer has the highest mortality. Different types of ovarian cancer vary significantly in their clinical and molecular characteristics and Epithelial ovarian cancer (EOC) is the most common subtype. Up to 20% of women with epithelial ovarian cancer have an inherited predisposition. The fallopian tubes are a potential source of high-grade serous cancer and risk reducing surgery can be an option. Routine screening with serum CA 125 and pelvic ultrasonography is still unproven. Diagnosis of ovarian tumours is usually made by pelvic ultrasonography and serum CA 125. The risk of malignancy index (RMI) 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 first line chemotherapy for epithelial ovarian cancer remains carboplatin with paclitaxel. BRAC mutation testing is frequently used to direct second line chemotherapy and molecular targeted treatments such as bevacizumab and PARP inhibitors have 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.

Keywords BRCA; carboplatin; debulking surgery; epithelial ovarian cancer; paclitaxel; palliative; RMI

Introduction

Ovarian cancer (OC) accounts for 6% of cancer deaths in women and has the highest mortality of gynaecological cancers. Different subgroups exhibit varied clinical and molecular characteristics and epithelial ovarian cancer is the commonest. High grade OC and high grade endometrioid OC have increased familial risk and in high risk groups risk reduction surgery is a valuable option. Screening in low risk groups is not useful whilst in the high-risk group its role is unclear.

Diagnosis is usually late and is made by pelvic ultrasonography (USS) and serum CA 125. Risk Malignancy index or Simple rule of USS is used to decide on treatment centre. The treatment is primary debulking surgery followed by adjuvant chemotherapy if needed. Neoadjuvant chemotherapy followed by interval debulking surgery and completion chemotherapy is as effective as primary surgery with reduced morbidity. Recent evidence is in favour of ultra-radical surgery aiming to excise all disease to improve outcome. Standard chemotherapy for epithelial ovarian cancer is intravenous carboplatin and paclitaxel. Intraperitoneal chemotherapy and newer molecular targeted treatments have been shown to be useful in select cases. Role of surgery for recurrent cases continues to be a matter of debate.

Incidence

The lifetime risk of OC in the developed world is 1–2% and 75% of cases are diagnosed above the age of 55 with a peak between 60 and 64 years. Five-year survival is 90% for stage 1 and <10% for stage IV but 70% of the cases are diagnosed at stage III. Despite significant improvement in the survival, the age adjusted survival rate is 42.9% which lags behind Australia, Canada, Norway and Sweden.

Risk factors

Breastfeeding, the oral contraceptive pill, non-steroidal anti-inflammatory drugs and also aspirin appear to protect against the development of OC. Endometriosis is associated with higher risk of OC. Ovarian stimulation drugs are associated with increased risk of borderline tumours. Family history of ovarian or breast cancer are strong predictors of BRCA gene mutation which increases OC.

Pathology and morphology

Based on embryological origin primary ovarian tumours can be classified as surface epithelial (coelomic), sex cord stromal (mesenchymal), and germ cell (mesonephric) (Table 1). Eighty percent are of epithelial origin, with serous carcinoma being the commonest. Secondary tumours from breast, stomach, endometrium and sarcomas and lymphomas are not uncommon.

Epithelial tumours

Seventy percent of epithelial tumours are high grade. Endometrioid and clear cell carcinoma's follow with 10% each, 5% are low grade serous carcinomas, while mucinous OC account for only 3%. Transitional (Brenner), mixed and undifferentiated tumours are very rare. It is becoming increasingly evident that these tumours behave as different entities.

High-grade and low-grade tumours arise from different entities and serous tumours seem to arise from dysplastic epithelium in the distal fallopian tube. High grade serous tumours are strongly associated with p53, BRCA 1&2 mutations and homologous recombination deficiency. Most commonly present at

Purushothaman Natarajan *MBBS MD MRCOG, Clinical Fellow in Gynaeoncology, Liverpool Women's Hospital, Liverpool, UK. Conflicts of interest: none declared.*

Sian E Taylor *MB ChB MD MRCOG, Consultant Gynaeoncologist, Liverpool Women's Hospital, Liverpool, UK. Conflicts of interest: none declared.*

John M Kirwan *MB ChB MRCOG, Consultant Gynaeoncologist, Liverpool Women's Hospital, Liverpool, UK. Conflicts of interest: none declared.*

Please cite this article in press as: Natarajan P, et al., Ovarian cancer: current management and future directions, Obstetrics, Gynaecology and Reproductive Medicine (2018), https://doi.org/10.1016/j.ogrm.2018.04.004

Classification of ovarian tumours

	Origin		
	Surface epithelium	**Sex cord stroma**	**Germ cell**
Types	Serous	Granulosa cell	Dysgerminoma
	Endometrioid	Thecoma	Yolk sac
	Clear cell	Fibroma	Embryonal Carcinoma
	Mucinous	Sertoli, Sertoli—Leydig	Choriocarcinoma
	Transitional cell	Steroid	Teratoma

Table 1

advanced stage and tend to be highly chemo-sensitive. Low grade serous tumours are associated with KRAS, BRAF, NRAS, HER2 ERBB2, PTEN, PIK3CA mutations, usually have a borderline component and tend to follow a more indolent course and 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 in 15%. 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 endometriosis and are usually unilateral with poor response to chemotherapy and poor prognosis.

In mucinous ovarian tumours it is evident that most of them are metastatic to the ovary from the gastrointestinal tract, usually the appendix. Primary mucinous tumours are associated with KRAS and HER2 mutations and are largely borderline with a small proportion being malignant and resistant to conventional chemotherapy.

Borderline ovarian tumours show histological features that are intermediate between benign and malignant tumours. Most of them are serous, mucinous and endometrioid are less common. They are found in younger age women, can spread beyond the ovary to produce non-invasive implants in the omentum or peritoneum and have late recurrences. It is probable that they represent premalignant disease for low grade ovarian carcinomas. Main treatment is surgery while the extent of this debatable and usually tailored to fertility concerns.

Primary peritoneal cancer is histologically indistinguishable from serous ovarian cancer and is diagnosed in the absence of any clear ovarian primary.

Sex cord-stromal tumours

Sex cord-stromal tumours account for approximately 7% of all malignant ovarian tumours. They arise from the hormone producing cells of the ovary and stromal fibroblasts. Granulosa cell tumours account for 70% of sex cord stromal tumours. Thecomas, fibromas, Sertoli—Leydig cell tumours are rare, usually unilateral and can produce androgen leading to virilization.

Granulosa cell tumours usually present at the sixth decade and less commonly in young or pre-pubertal women. They are usually unilateral and can secrete sex hormones, mainly oestrogen. Excess of oestrogen can lead to endometrial hyperplasia and cancer in the older group or precocious puberty in the pre-pubertal group.

The vast majority are diagnosed as early stage with a favourable prognosis. Late recurrences can also occur. Fertility sparing surgery is suggested for younger women while chemotherapy (bleomycin, etoposide, and cisplatin), is used for advanced disease or recurrences.

Malignant germ cell tumours

The commonest malignant germ cell tumour is dysgerminoma. Dysgerminoma's occur mainly in adolescence and early adulthood and can be bilateral in up to 20%. They can produce high levels of LDH. Since over 60% are confined to one ovary at diagnosis, fertility sparing surgery with unilateral salpingo-oophorectomy or even ovarian cystectomy in selected cases is an option. Dysgerminomas spread through the lymphatic system and though highly radiosensitive, platinum-based chemotherapy is preferable due to fertility preservation.

Yolk sack tumour, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma and teratoma tumours are other type of germ cell tumours and treated with chemotherapy (bleomycin, etoposide, and cisplatin). Cure rates are approaching 100% in early stage and 75% in advanced disease.

Screening

The best currently available modalities for screening are still those of pelvic ultrasound scan and the tumour marker CA 125 (Cancer 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, β-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.

Current evidence shows that screening for OC fails to decrease mortality but does increase unnecessary surgery rate (PLCO cancer screening trial). Long-term large multicentre trials (UKTOCS: United Kingdom Trial of Ovarian Cancer Screening and UKFOCS: United Kingdom Familial Ovarian Cancer Screening) has shown no reduction in mortality on primary analysis but a possible reduction in prevalent cases after 7 years of follow-up. Despite limitations and potential risks, ovarian surveillance is offered to high risk patients.

Please cite this article in press as: Natarajan P, et al., Ovarian cancer: current management and future directions, Obstetrics, Gynaecology and Reproductive Medicine (2018), https://doi.org/10.1016/j.ogrm.2018.04.004