Ovarian Cancer

Lack of early-stage symptoms is the hallmark of this insipid disease

Why is ovarian cancer so deadly?

Between 85-90% of all malignant ovarian tumours arise from epithelial ovarian cells, while the remaining originate from either germ cells or sex cord stromal cells. Epithelial ovarian cancer (EOC) is the most lethal of all gynecological cancers and is the fifth leading cause of cancer death in women, after breast, lung, colon and stomach. The poor survival rate is due to lack of effective screening and the absence of symptoms during early-stage disease.

Approximately two-thirds of women with EOC typically present with metastatic disease that's frequently associated with only vague symptoms. The pathogenesis and evolution of EOC is poorly understood and little is known about whether dysplastic precursors exist to detect the disease earlier. The malignant transformation of normal ovarian surface epithelial cells is believed to be caused by genetic, molecular and hormonal alterations that disrupt cell proliferation, apoptosis, senescence and DNA repair.1

What are the risk factors?

In the general population, the lifetime risk of a woman developing EOC is 1 in 70. Most ovarian cancers occur in postmenopausal women at a median age of about 60 years. The majority of EOCs (90%) are considered to be sporadic events resulting from the accumulation of genetic damage over a lifetime. Up to 10% have an autosomal dominant hereditary predisposition and are associated with germ line mutations of BRCA1 and BRCA2 genes, which account for 95% of hereditary ovarian carcinomas.2 Among the Ashkenazi Jewish population, three specific mutations (185delAG or 5382insC in the BRCA1 gene and 6174deIT in the BRCA2 gene) occur in a substantial proportion of high-risk families. Carriers of these mutations have a lifetime risk of 55-85% for breast cancer and 15-60% for ovarian cancer.3 Since those patients with known BRCA1 and BRCA2 mutations are relatively few, it's possible to identify individuals at higher risk based on a personal and family history of cancer (see Table 1).

Protective factors that diminish the risk of ovarian cancer include multiparity and taking the oral contraceptive pill (OCP). The overall estimated protection offered by the OCP is approximately 40% in ever users, but increases to 50% for women who've taken them longer than five years. This important protective effect is present even in those with a hereditary risk for developing disease.4

What are the common signs and symptoms?

Given the location of the ovaries deep within the pelvis, most patients with early disease confined to the ovaries have no symptoms at all. As a result, affected women typically present when the cancer is at a more advanced stage, with disseminated disease in the upper abdomen. The cancer tends to remain and recur in the peritoneal cavity for the majority of patients, yet malignant pleural effusion isn't uncommon. While the most common sign of ovarian cancer is abdominal distension, frequent symptoms consist of bloating, anorexia, fatigue, gastrointestinal upset, vague abdominal pain and a change in bowel function (see Table 2). Since the presentation is often vague, ovarian cancer can mimic other problems related to the gastrointestinal or genitourinary system, which may contribute to a delay in diagnosis.

Why is there no accepted screen for ovarian cancer?

The objective of screening for ovarian cancer is to detect and surgically treat early-stage disease when there is the highest likelihood of a cure.

The most widely used serologic marker for EOC is the cancer antigen 125 (CA-125). A serum CA-125 of 35 U/mL is usually accepted as the upper limit of normal. The interest in CA-125 as a screening test is derived from the fact that about 83% of women with EOC have an elevated CA-125.5 Increased levels are found in more than 90% of women with advanced-stage disease, but only 50% of women with stage I disease. Those with mucinous and borderline tumours are also associated with lower levels of CA-125.6

CA-125 is most useful when monitoring the evolution of disease, particularly, in response to treatment, but it lacks the specificity and positive predictive value to be a useful screening tool. The high false-positive rate is due to elevated levels in other malignancies (pancreas, breast, bladder, liver, lung), benign conditions (diverticulitis, uterine leiomyomas, endometriosis, benign ovarian cysts, tubo-ovarian abscess, ectopic pregnancy) and physiological states (pregnancy, menstruation).

Transvaginal ultrasound has also been studied as a screen for ovarian cancer, including the role of colour Doppler imaging. The largest cohort study on the use of ultrasound alone screened over 23,000 women annually, resulting in 95 women undergoing surgery and the detection of seven malignant ovarian cancers.7 The positive predictive value, however, was only 7.4%.

In a pilot randomized controlled trial by Jacobs, over 22,000 women were randomized to annual screening for three years with CA-125 followed by endovaginal ultrasound vs no screening.8 It was determined that for every 10,000 women undergoing annual screening, 800 will have an ultrasound done for an elevated CA-125, 30 will undergo surgery, and of these, six will have ovarian cancer, of which, three will be early stage where there's a greater likelihood of a cure. In addition, 24 women will have unnecessary surgery, while many others will experience the anxiety associated with an abnormal test result.

To date, studies lack the sensitivity, specificity and positive predictive value to recommend CA-125 and ultrasound as effective screening options for ovarian cancer. There's also no good evidence to suggest that CA-125 and ultrasound reduce the mortality rate of ovarian cancer, either in the general population or among genetically predisposed women.

How is a patient diagnosed and staged?

The gold standard for establishing the presence or absence of ovarian cancer is oophorectomy. Given clinical suspicion, the diagnosis of EOC is made at the time that a surgical staging procedure is performed with histopathological confirmation. This generally consists of exploratory laparotomy through a midline incision, allowing the palpation and visualization of peritoneal surfaces, followed by bilateral salpingo-oophorectomy, hysterectomy, omentectomy, cytology and directed biopsies (see Table 3).

In patients with suspected early-stage disease, pelvic and para-aortic lymphadenectomy is advocated as up to 30% of patients with apparent stage I disease may have occult lymph node metastases.9 Laparoscopic surgical staging for women with presumed early-stage EOC is being performed with increasing frequency with the aim to gather sufficient clinical data to support this approach in certain patients. The main concerns regarding laparoscopic staging include delay to surgery (after diagnosis on frozen section), port-site metastases, tumour spillage and incomplete resection.10

How is ovarian cancer treated?

The standard therapy for advanced ovarian cancer is a combination of cytoreductive surgery (with the aim to leave less than 1-2 cm of residual tumour) and a platinum and taxane-based chemotherapy regimen. The timing of cytoreductive surgery varies, depending on disease presentation, with a now well-accepted standard of neo-adjuvant chemotherapy to decrease tumour burden and facilitate primary surgical efforts. The response to first-line chemotherapy with carboplatin and paclitaxel given for six cycles every three weeks is 80%.11 Unfortunately, most patients with advanced disease will have a recurrence, with a mean progression-free survival rate of only 18 months.

Response to second-line chemotherapy is directly related to the treatment-free interval. Patients with recurrent disease may be re-treated with a platinum-based regimen (carboplatinum/ paclitaxel). If a patient relapses after 12 months, re-treatment with the initial regimen can lead to response rates of up to 70%. However, if the treatment-free interval is less than six months, the response rate falls dramatically to 10-15%. These latter tumours are considered platinum-refractory and may be treated with alternate second-line agents, though the response rate is still about 15%.

What if there's resistance to chemotherapy?

Patients with recurrent disease are often faced with resistance to a carboplatinum-based regimen. The management objective in these individuals is to balance the prolongation of progression-free interval with reduced morbidity, favouring quality of life. Aside from platinum, drug classes used for relapsing disease include anthracyclines (liposomal doxorubicin), topoisomerase inhibitors (etoposide, topotecan), taxanes and nucleoside analogues (gemcitabine). The role of a second operation in ovarian cancer is limited and usually reserved for palliative bowel resection/diversion or isolated recurrent disease associated with a long recurrence-free interval and a good performance status. Similarly,

radiation therapy may be considered in some cases with a well-localized tumour burden.

What are key prognostic factors?

Disease stage is the most important prognostic factor in ovarian cancer. Approximately 70% of patients present with stage III and IV disease resulting in a five-year survival of about 30%.12 Women with stage I disease, however, have a high likelihood of cure (80-90% five-year survival rate). Stage I tumours are more likely to be either well (54%) or moderately (28%) differentiated, whereas stage III tumours are often poorly differentiated.

Early-stage disease has a preponderance of mucinous, clear-cell and endometrioid histologies, whereas advanced disease is most likely to have a papillary serous histology. Papillary serous is the most common histological subtype and commonly presents with disease beyond the ovaries at diagnosis. Mucinous tumours appear to develop from their benign and borderline counterparts, while endometrioid and clear cell histologies are more likely associated with endometriosis and prolonged estrogen-replacement therapy.

An endometrioid histology has a relatively favourable prognosis and malignant transformation of endometriosis has been reported to occur in 0.7-1.0% of patients.13 It's still controversial whether early-stage clear cell tumours indicate a worse prognosis. The strongest clinician-driven predictor of survival is optimal surgical outcome, which results in residual disease that is no greater than 1-2 cm per tumour nodule.14 Patients in whom the remaining tumour is larger vs smaller than 2 cm have a median survival rate of 12-16 months compared to 40-45 months, respectively.15 To assure a maximal primary surgical effort, it's recommended that women are referred to centres that have experience in performing cytoreductive surgery.

In advanced-stage ovarian cancer, there is a suggestion -- albeit inconsistent -- that over-expression of a mutant p53 gene may be linked to a worse survival. Overall, about 50% of advanced EOCs are correlated with p53 mutations, which is a possible factor contributing to chemotherapy resistance.16

What does the future hold?

Over the last several decades, management has focused primarily on surgical and chemotherapeutic options, though, unfortunately, with little change in overall survival. Recent advances in the study of ovarian cancer have explored the molecular aspects of this disease and hold exciting promise for both early detection and new treatment options.

The recent explosion of genomics, transcriptional profiling and proteomic techniques, which characterize tumours at the DNA, RNA and protein levels, may reveal new clinical markers for ovarian cancer screening. Such technology has proved useful in detailing a molecular profile of various subtypes of ovarian cancer, and the information may one day be correlated with a patient's particular genotype. This holds great potential to tailor therapy regimens to match treatment with a patient's specific disease profile. Furthermore, the malignant transformation in EOC has been associated with multiple molecular changes such as the up-regulation of tyrosine kinases, activation of proto-oncogenes, mutations of tumour suppressor genes and mutator genes, as well as increased activity of proteolytic enzymes.17 Studies are currently in effect to exploit these changes.

This has proven useful in the development of novel molecular therapies that target the function of a specific gene, protein or molecular pathway, and clinical trials are underway to test their efficacy in patients. In addition, molecular advances have made progress in understanding drug resistance and may be used to apply new therapeutic strategies to overcome chemoresistance in ovarian cancer.

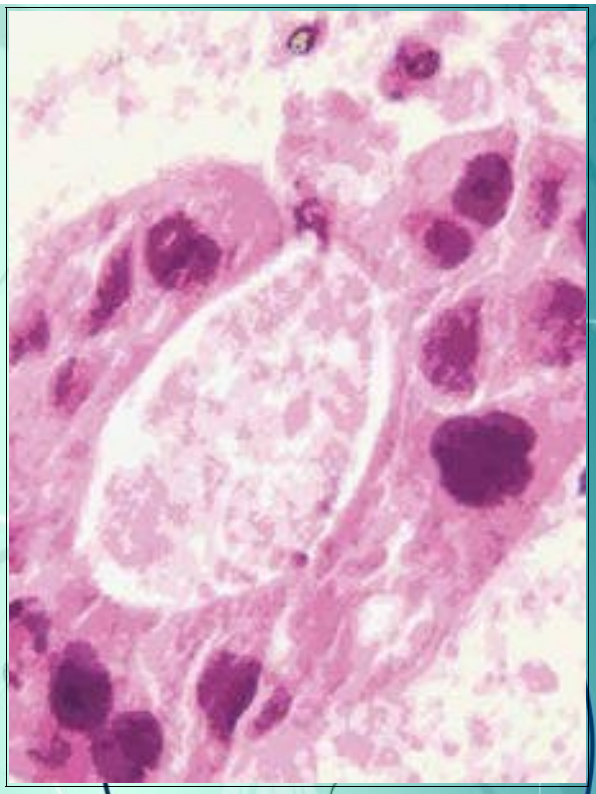

Table 1. Risk factors for ovarian cancer

- two or more close relatives, i.e. a mother, sister, or aunt, who've had ovarian and/or breast cancer, particularly if there's:
- a breast cancer diagnosis before age 40
- the presence of breast or ovarian cancer in the same woman
- bilateral breast cancer
- breast cancer in a male relative
- family history of malignancy, e.g. ovarian, breast or colon
- personal history of cancer, particularly breast, uterine or colon
- Ashkenazi Jewish, French Canadian or Icelandic descent
- known BRCA1 or BRCA2 mutation

Table 2. Common symptoms of ovarian cancer

- pelvic or abdominal discomfort, i.e. constant fullness or bloating
- gas, nausea or indigestion
- changes in bladder or bowel habits
- unexplained weight gain or loss
- fatigue
- difficulty breathing (patients will commonly have many ascites)

Table 3. Ovarian cancer staging

Stage	Characteristics
I	tumour limited to the ovaries
II	tumour involving one or both ovaries with pelvic extension
III	tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes; superficial liver metastases
IV	tumour involving one or both ovaries with distant metastases; cytologically proven pleural effusion; parenchymal liver metastases