

## OVARIAN CANCER

Ovarian cancer is the leading cause of death from gynaecologic cancer because it is difficult to detect before it disseminates. In Australia, there are about 1500 new cases of ovarian cancer diagnosed each year, and about 800 deaths. Most women with ovarian cancer are in the fifth or sixth decade of life.

The cause of ovarian cancer is unknown. The patient characteristics found to be associated with an increased risk for epithelial ovarian cancer include late age at menopause, family history of cancer of the ovary, breast or bowel, and prolonged intervals of ovulation uninterrupted by pregnancy. There is an increased prevalence of ovarian cancer in women who have had no children.

About 10% of epithelial ovarian cancers occur in women with a hereditary predisposition. In women with hereditary cancers, two or more first-degree relatives on either the paternal or maternal side typically have had breast or ovarian cancer. The pattern of inheritance is autosomal dominant and is associated with breast cancer in young women. The two abnormal genes associated with the breast – ovarian cancer syndrome are called BRCA1 and BRCA2. The Lynch II syndrome, (nonpolyposis colorectal cancer syndrome), is associated with mutations in the mismatch repair genes. Cancers of the ovary, breast, colon, stomach, pancreas, and endometrium are seen in the families of these individuals.

The use of oral contraceptives has been found to protect against ovarian cancer, possibly because of suppression of ovulation. It has been postulated that incessant ovulation may predispose to malignant transformation in the ovary.

Patients with a known germ line mutation (e.g., BRCA1 and BRCA2 mutations) may be offered prophylactic salpingo-oophorectomy (removal of tubes and ovaries) once childbearing has been completed, and this operation is highly protective for ovarian and fallopian tube cancers. Indeed, the risk of subsequent breast cancer is also significantly reduced in these women. There is still a small risk of peritoneal carcinoma after prophylactic salpingo-oophorectomy.

The perineal use of asbestos-contaminated talc has been linked to the development of epithelial ovarian cancer. This possibility remains controversial, although tubal ligation and hysterectomy are both associated with a decreased risk of the disease.

## SCREENING FOR OVARIAN CANCER

Population screening for ovarian cancer is not feasible because ultrasonography and available tumour markers, for example, CA 125, lack accuracy for early-stage disease. CA 125 is more useful in postmenopausal women because false-positive measurements occur commonly in premenopausal women in association with endometriosis, pelvic inflammatory disease, or uterine fibroids. Patients with a strong family history of epithelial ovarian cancer may benefit from surveillance with serial transvaginal ultrasonography and serum CA-125 titers.

## CLINICAL FEATURES

### SYMPTOMS

In early-stage disease, the patient may complain of vague abdominal pain, lethargy or irregular periods if she is premenopausal. Symptoms of a mass compressing the bladder or rectum, such as urinary frequency or constipation, may bring the patient to a physician. Sometimes the patient complains of a lower abdominal or pelvic “fullness” or of painful intercourse. Only rarely does a patient present with acute symptoms, such as pain secondary to torsion, rupture, or intracystic haemorrhage.

In advanced-stage disease, patients most often present with abdominal pain or swelling. The latter may be from the tumour itself or from associated ascites. On careful questioning, there has usually been a history of vague abdominal symptoms, such as bloating, constipation, nausea, dyspepsia or loss of appetite. Premenopausal patients may complain of irregular menses or heavy vaginal bleeding.

### PREOPERATIVE EVALUATION

The diagnosis of ovarian cancer requires a laparotomy or laparoscopy. In patients with significant intestinal symptoms, a colonoscopy should be obtained to rule out a primary colonic cancer with ovarian metastasis. Similarly, an upper endoscopy is important if there are significant stomach symptoms. Breast cancer may also metastasize to the ovaries, so bilateral mammograms should be obtained if there are any suspicious breast masses.

The tumour-associated antigen CA 125 is elevated in only about 50% of women with stage I ovarian cancer. When serum CA 125 titre is elevated, it is useful for monitoring the clinical course of the disease.

### DIFFERENTIAL DIAGNOSIS

Ovarian malignancies must be differentiated from benign tumours and functional cysts of the ovaries. In addition, a variety of gynaecologic conditions can simulate a neoplastic process, including tubo-ovarian abscess, endometriosis, and a pedunculated uterine fibroid. Non gynaecologic causes of a pelvic tumour must also be excluded, such as an inflammatory bowel condition (eg diverticulitis) or a bowel cancer.

### MODE OF SPREAD

Ovarian cancer typically spreads by shedding cells that disseminate and implant throughout the abdominal cavity. Metastases are commonly seen on the diaphragm, liver capsule, and in the omentum. Implants are also common on the bowel.

Lymphatic dissemination to the pelvic and para-aortic nodes is common, particularly with advanced disease. Blood borne metastases are not common, and spread to the liver and lungs are seen in only about 2% of patients at initial presentation.

## STAGING

The standard staging system for ovarian cancer is presented in Table 1. **Ovarian cancer is surgically staged** according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system.

Even though all microscopic disease may appear to be confined to the ovaries at the time of laparotomy, microscopic spread may have already occurred; thus, patients must undergo a thorough “surgical staging.” Procedures necessary to stage ovarian cancer are shown in Box 1.

**Table 1. International Federation of Gynaecology and Obstetrics (FIGO) staging for primary carcinoma of the ovary**

<b>Stage I</b>	Growth limited to the ovaries.
Stage Ia	Growth limited to one ovary; no ascites. No tumour on the external surface; capsule intact.
Stage Ib	Growth limited to both ovaries; no ascites. No tumour on the external surfaces; capsules intact.
Stage Ic	Tumour either stage Ia or Ib but with tumour on the surface of one or both ovaries or with ruptured or with ascites present containing malignant cells or with positive peritoneal washings.
<b>Stage II</b>	Growth involving one or both ovaries with pelvic extension.
Stage IIa	Extension or metastases, or both, to the uterus or tubes, or both.
Stage IIb	Extension to other pelvic tissues.
Stage IIc	Tumour either stage IIa or IIb but with tumour on the surface of one or both ovaries or with capsule or capsules ruptured or with ascites present containing malignant cells or with positive peritoneal washings.
<b>Stage III</b>	Tumour involving one or both ovaries with peritoneal implants outside the pelvis or retroperitoneal or inguinal nodes, or both. Superficial liver metastasis equals stage III.
positive	Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.
Stage IIIa	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIb	Tumour of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter. Nodes negative for disease.
Stage IIIc	Abdominal implants $\geq$ 2cm in diameter or positive retroperitoneal or inguinal nodes, or both.
<b>Stage IV</b>	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

### Box 1. Requirements for staging operation

#### MULTIPLE CYTOLOGIC ASSAYS

Free ascitic fluid, if present  
Peritoneal “washings” (50mL of normal saline)

#### MULTIPLE INTRAPERITONEAL BIOPSIES

##### *Pelvis*

Cul-de-sac peritoneum  
Bladder peritoneum

Pedicles of infundibulopelvic ligaments  
Any adhesions

**Abdomen**

Both paracolic gutters  
Bowel serosa and mesenteries  
Omentum  
Any adhesions

**EXTRAPERITONEAL BIOPSIES**

Pelvic and para-aortic lymph nodes

\*Procedures performed in patients with no visible evidence of metastatic disease.

**CLASSIFICATION**

The histologic classification of ovarian neoplasms is listed in Table 2. These lesions fall into four categories according to their tissue of origin. **Most ovarian neoplasms (80% to 85%) are derived from coelomic epithelium and are called epithelial carcinomas.** Less common tumours are derived from primitive germ cells, specialized gonadal stroma, or non-specific mesenchyme. In addition, the ovary can be the site of metastatic carcinomas, most often from the gastrointestinal tract or the breast.

**Table 2. Histogenetic classification of primary ovarian cancers**

Derivation	Type of Tumour
Coelomic epithelial origin (80%–85%)	“Common” epithelial tumours; Serous carcinoma Mucinous carcinoma Endometrioid carcinoma Clear cell (mesonephroid) carcinoma
Germ cell origin (10%–15%)	Immature teratoma Dysgerminoma Endodermal sinus tumour Embryonal carcinoma Choriocarcinoma
Specialized gonadal-stromal origin (3%–5%)	Mixed germ cell tumours Granulosa cell tumour Sertoli-Leydig tumours Sertoli cell tumour
Nonspecific mesenchymal origin (fewer than 1%)	Lymphoma Sarcoma

Approximately 5% to 10% of malignant serous tumours are of low malignant potential (borderline) whereas 20% of malignant mucinous tumours fall into this category.

## MANAGEMENT OF EPITHELIAL OVARIAN CANCER

The initial approach to all patients with ovarian cancer is surgical exploration of the abdomen and pelvis.

### Early-Stage Disease

Definitive diagnosis requires removal of the ovarian tumour and frozen section. In patients with no gross evidence of disease beyond the ovary, the standard operation is total abdominal hysterectomy, removal of both tubes and ovaries, removal of the omentum, and thorough surgical staging, as shown in Box 1. Patients who wish to preserve fertility may have removal of the affected ovary and tube only. In patients with grade 1 or grade 2 tumours confined to one or both ovaries after surgical staging, no further treatment is necessary. Patients with poorly differentiated (grade 3) tumours are subsequently treated with chemotherapy.

### Advanced-Stage Disease

In patients with advanced disease, cytoreductive surgery (“debulking”) is required. The objectives are to remove the primary tumour and all of the metastases, if possible. If all obvious disease cannot be removed, an attempt should be made to reduce individual tumour nodules to 1cm or less in diameter. Patients in whom this goal is achieved are said to have had “optimal” cytoreduction, which can be achieved in about 70% of patients. In addition to a total abdominal hysterectomy, removal of both tubes and ovaries, omentectomy, and resection of peritoneal metastases, optimal cytoreduction may necessitate bowel resection; therefore, all patients having surgery for suspected ovarian cancer should have a bowel preparation preoperatively.

In patients who are medically unfit or have a poor performance status, usually because of a large pleural effusion and massive ascites, it may be prudent to give two or three cycles of chemotherapy before undertaking radical surgery. If the disease does not respond to chemotherapy, as evidenced by the failure to resolve the malignant effusions, the patient should be offered palliative care only. Usually, the effusions resolve completely, and an “interval” cytoreductive operation can be safely undertaken.

Following primary cytoreductive surgery, combination chemotherapy is given, most commonly using carboplatin and paclitaxel. During chemotherapy, the patient’s response is monitored with serial CA 125 levels. If the values rise within 12 months, it is advisable to change to second-line drugs, such as caelyx, topotecan, etoposide, gemcytabine, or experimental chemotherapeutic agents. If the progression-free interval has been greater than 12 months, the patient may respond to further paclitaxel or carboplatin chemotherapy.

### Prognosis

Patients with stage I disease have 5-year survival rates of 75% to 95%, depending on the histologic grade.

Almost all patients with carefully staged Ia grade 1 ovarian cancer are cured surgically, whereas the 5-year survival rate for patients with poorly differentiated bilateral lesions is as low as 75%. Despite aggressive primary surgery and combination chemotherapy, the 5-year survival rate for patients with advanced-stage disease is about 20%, although the median survival is between 2 and 3 years.

Patients who have borderline ovarian tumours can be expected to have a prolonged survival. If the disease is confined to the ovary, the vast majority of tumours never recur. Five- and 10-year survival rates are 95% to 100%, but late recurrences may occur, and 20-year survival rates are approximately 85% to 90%.

## GERM CELL TUMOURS

Germ cell tumours of the ovary account for only about 2% to 3% of all ovarian malignancies. They occur predominantly in young patients and frequently produce either human chorionic gonadotropin (hCG) or  $\alpha$ -fetoprotein (AFP), which serve as tumour markers. The most common germ cell tumours are the dysgerminoma and immature teratoma. Endodermal sinus tumours, embryonal tumours, and nongestational choriocarcinomas are less common. Mixed germ cell tumours are not uncommon.

## DYSGERMINOMAS

Dysgerminomas occur predominantly in children and young women. About 10% are bilateral. In about two-thirds of patients, the disease is confined to the ovaries at the time of diagnosis. Pure dysgerminomas do not produce the tumour markers hCG and AFP, but commonly produce lactate dehydrogenase (LDH).

## IMMATURE TERATOMAS

Immature teratomas are the second most common malignant ovarian germ cell tumour. About 75% of malignant teratomas are encountered during the first two decades of life. Bilateral lesions are rare. Like other germ cell tumours, immature teratomas grow fairly rapidly, cause pain early, and are found confined to the ovary in about two-thirds of cases at the time of diagnosis. Pure immature teratomas do not produce hCG or AFP.

## OTHER GERM CELL TUMOURS

The endodermal sinus tumour is a rare malignancy. It is also referred to as a *yolk sac* tumour. Endodermal sinus tumours produce AFP, which can serve as a useful serum marker for this tumour. Embryonal carcinomas produce both hCG and AFP, whereas choriocarcinomas produce hCG only. All occur in children and young women, and all grow rapidly. Bilateral tumours are rare.

## Treatment

Because they occur in young females and are very sensitive to chemotherapy, germ cell tumours should be treated by surgical removal of the primary tumour, with preservation of the uterus and opposite ovary.

Chemotherapy, usually with bleomycin, etoposides and cisplatin (BEP), is given for all tumours except for stage 1A dysgerminoma and stage 1A grade 1 immature teratomas. These tumours can be treated with surgery alone.

## Prognosis

The prognosis for germ cell tumours is excellent with modern chemotherapy, with survival rates in major centres better than 90%

## SPECIALIZED GONADAL-STROMAL TUMOURS

A group of relatively uncommon tumours is derived from the specialized ovarian stroma. As such, they are often able to produce hormones. **Estrogen and progesterone are typically associated with granulosa-cell tumours, whereas testosterone and other androgens may be secreted by many Sertoli-Leydig cell tumours.**

## Treatment

Most stromal tumours occur in postmenopausal women, and are best treated by a total abdominal hysterectomy and removal of both tubes and ovaries.

## Prognosis

Granulosa cell tumours, which tend to grow slowly, are usually confined to one ovary at the time of diagnosis. The 5-year survival rate is approximately 90% for stage I disease. Recurrences are usually detected late and may result in death 15 to 20 years after removal of the primary lesion.

## METASTATIC CANCERS

About 4% to 8% of ovarian malignancies are metastatic, most commonly from either the gastrointestinal tract or the breast.

## FALLOPIAN TUBE CANCER

Primary carcinoma of the fallopian tube accounts for only 0.1% to 0.5% of gynaecologic cancers and is diagnostically confused with ovarian carcinoma. **Most are adenocarcinomas, but sarcomas and mixed tumours can occur.** Bilateral carcinomas are seen in 10% to 20% of patients.

## Clinical Features

Clinically, patients can present with a vaginal discharge that is typically watery in nature, as well as vaginal bleeding, pelvic pain, or some combination of symptoms. In postmenopausal patients, the vaginal discharge may be yellow or watery. A fallopian tube cancer should be suspected in a postmenopausal patient whose bleeding or abnormal cytologic findings are not explained by endometrial or endocervical curettage. In most patients, the diagnosis is not made preoperatively.

## Treatment

The treatment for fallopian tube carcinoma is total abdominal hysterectomy, removal of both tubes and ovaries, and omentectomy. Surgical staging should be performed in patients whose disease appears to be confined to the pelvis, and cytoreductive surgery is appropriate in patients with metastatic disease. Postoperatively, combination chemotherapy, including carboplatin and paclitaxel, is usually used for patients with stages II–IV disease.

## Prognosis

The prognosis for fallopian tube carcinoma is similar to that for ovarian cancer.