**Malignant Ovarian tumours:** **Ass Prof Dr Ban Hadi**

 F.I.B.O.G. 2021



**LEARNING OBJECTIVES:**

**Fifth year students should be able to:**

1. Describe the types of malignant ovarian tumours
2. Summarize the important points in history and examination to reach the diagnosis
3. Interpret ultrasound and investigations results
4. Predict the management option for different case scenarios according to their presentation

 Ovarian cancer is the second most common gynaecological malignancy and the major cause of death from gynaecological cancer in the UK.

 When detected in its early stages, ovarian cancer has an excellent prognosis. The dismal overall survival rates from ovarian cancer reflect the advanced stage at which most women present.

* **Incidence**
* The lifetime risk of developing ovarian cancer in the general population is 1.4%, and the **mean age** of presentation is **64 years**.
* Ovarian cancer is more prevalent in higher income nations. There are variations in incidence with ethnicity; white women have the highest incidence, whereas Asian women have a lower incidence.
* Ovarian cancer is rare in young women and only 3% of ovarian cancers occur in women under 35 years.
* There is a significant genetic aspect to ovarian cancer. It is recognized that women with hereditary cancer present early, with a mean age at diagnosis of 54 years.
* It should be noted that less than 20% of adnexal masses in premenopausal women are found to be malignant; in postmenopausal women this increases to around 50%.
* **Histological Classification of ovarian cancer:**

**Primary and secondary tumours**

**1. Epithelial ovarian tumours** (80%)

Serous

Endometrioid

Clear cell

Mucinous

**2. Sex cord stromal tumours** (10%)

Granulosa cell

Sertoli–Leydig

Gynandroblastoma

**3. Germ cell tumours** (10%)

Dysgerminoma

Endodermal sinus (yolk sac)

Teratoma

Choriocarcinoma

**4. Metastatic** (including Krukenberg tumours) are ovarian metastases associated with primary cancers of the colon, stomach and breast

**Epithelial tumours of the ovary**:

The majority of ovarian neoplasia both benign &malignant arises from the ovarian surface epithelium. They are therefore mesothelial in nature derived from the coelamic epithelium overlying the embryonic gonadal ridge, from which develop mullerian & wolffian structures: therefore: this may result in development along:-

1. Endocervical= mucinous cyst adenocarcinoma.
2. Endometrial= endometrioid.
3. Tubal = serous cyst adenocarcinoma.
4. Uroepithelial= Brenner tumour

 Epithelial ovarrian tumours can be benign, malignant or borderline.

Approximately 10% of epithelial tumours are classified as **borderline ovarian tumours** (BOTs). These tumours are well differentiated, with some features of malignancy (nuclear pleomorphism, cellular atypia) but do not invade the basement membrane.

BOTs spread to other abdominopelvic structures (peritoneum, omentum) but do not often recur following initial surgery.

The majority of BOTs are **serous tumours**.

**Mucinous BOT**s may actually arise from appendiceal carcinomas of low malignant potential and can be associated with pseudomyxoma peritoneii.

**High-grade serous carcinomas** account for around 75% of all epithelial ovarian cancers; **Mucinous** and **Endometrioid tumours** are less common, accounting for 10%, followed by **Clear cell carcinomas**.

High grade serous tumours are characterized histologically by concentric rings of calcification, known as ‘psammoma bodies’.

Mucinous carcinomas are generally large multiloculated tumours associated with

pseudomyxoma peritoneii.

Endometrioid carcinomas are similar in histological appearance to endometrial cancer, are associated with endometriosis in approximately 10% of cases and also a synchronous separate endometrial cancer in 10–15%. They tend to be well differentiated and are associated with a better survival than high-grade serous carcinomas.

Clear cell carcinomas can also arise from endometriosis and are characterized histologically by clear cells, much like renal cancer.

* **Risk factors for ovarian cancer:**
* **Increased risk :**

Nulliparity, Intrauterine device, Endometriosis, Smoking, Obesity, Early menarche, Late menopause, White race, Increasing age, Family history, American and Europe residence.

* **Decreased risk:**

Multiparity, Combined oral contraceptive pills, Tubal ligation, Salpingectomy, Hysterrectomy.

The ‘**incessant ovulation’ theory** holds that the repeated damage to the ovarian surface epithelium that occurs at ovulation increases the risk of mutations that drive ovarian carcinogenesis. Excess gonadotrophin secretion is also thought to drive

tumorigenesis through oestrogen-stimulated epithelial proliferation and subsequent malignant transformation.

* **Genetic factors in ovarian cancer**:

It is estimated that at least 10–15% of women with epithelial ovarian cancer have a hereditary predisposition. Women with mutations in ***BRCA1, BRCA2***and **Lynch** syndrome have an increased lifetime risk of epithelial ovarian cancer.

The lifetime risk in the general population is one in 70 (1.4%). This rises to 1 in 20 (5%) if women have one family member affected by a defect in one of these genes and further increases to 40–50% if two first-degree relatives are affected

The most common hereditary cancer is the breast ovarian cancer syndrome (BRCA), accounting for 90% of the hereditary cancers. This syndrome is due to a mutation of tumour suppressor genes *BRCA1* (80%) and *BRCA2* (15%).

Lynch syndrome is hereditary non-polyposis colorectal cancer (HNPCC) and

is associated with endometrial cancer and a 10% lifetime risk of ovarian cancer.

* **Prevention of ovarian cancer:**

Women who test positive for a BRCA mutation are offered risk-reducing measures:

**1. Prophylactic bilateral salpingo-oophorectomy BSO** when they have completed their families. This can usually be performed laparoscopically.

 It is important to carry out risk-reducing surgery prior to the age-related surge in ovarian cancer observed in BRCA mutation carriers, which is younger in

*BRCA1* (mid 30s) than *BRCA2* patients (early 40s).

Another suggestion for risk reduction builds on the theory that BRCA-associated ovarian cancers actually originate in the Fallopian tube; hence performing

**2. Bilateral salpingectomy with delayed oophorectomy** in the 30s and early 40s may offset the morbidity associated with a surgical menopause in young women while reducing the risk of cancer.

Recent data indicate that the opportunistic removal of the Fallopian tubes during hysterectomy for benign indications also reduces ovarian cancer risk in women at average lifetime risk of ovarian cancer.

Other procedures associated with ovarian cancer risk reduction include:

**3. Tubal ligation (sterilization)** and

**4. Hysterectomy with ovarian conservation**.

**5. Chemoprevention** using the combined oral contraceptive pill (COCP) reduces ovarian cancer risk by up to 50% in both BRCA mutation carriers and women at average risk of ovarian cancer.

* **Screening:**

Screening using **transvaginal ultrasound** scan (TVUSS) and **CA125** measurement has not been shown to improve survival in women with a familial predisposition to ovarian cancer. This is because the high grade serous tumours that are associated with BRCA mutation carrier status develop rapidly and most are at an advanced stage before they can be picked up by screening.

**Diagnosis:**

1. **History: Age, Symptoms and risk factors**

**Age:** the **mean age** of presentation is **64 years**

**Symptoms:** Most women with ovarian cancer have non-specific and often

vague symptoms. The difficulty with clinical diagnosis is the main reason that patients with ovarian cancer present with late stage disease (66% present with stage 3 disease or greater), and this has a dramatic effect on survival.

**The most common symptoms** are:

• Increased abdominal girth/bloating.

• Persistent pelvic and abdominal pain.

• Difficulty eating and feeling full quickly.

Other symptoms such as change in bowel habit, urinary symptoms, back ache, irregular bleeding and fatigue occur frequently

**Risk factors: for ovarian cancer**

1. **Examination:**

**General:** General health, BMI, pallor, jaundice in case of metastasis

 Lymph nodes examination neck and groin, left supraclavicular lymph node is suggestive of malignancy, enlarged Virchow's node (Troissier's sign )

 Leg oedema in cases of tumours due to pressure effect or invasion of pelvic vessels

 Breast, neck and chest examination. Pleural effusion goes with malignancy

**Abdominal examination** may reveal a fixed, hard mass arising from the pelvis so that we can not palpate below it. In combination with the presence of ascites demonstrated by shifting dullness and/or a fluid thrill, a diagnosis of ovarian cancer is highly likely.

**Pelvic examination**: Early-stage ovarian cancer is difficult to diagnose due to the position of the ovary, but an adnexal mass may be palpable in a slim woman. Features of malignancy are fixed, hard, bilateral adnexal masses invaded other organs.

1. **Investigations**

**1.Ultrasound**: TVUSS is the initial imaging modality of choice to check for pelvic

pathology. A pelvic mass characteristics that are suggestive of malignancy:

* Consistency, the presence of solid elements, as **papillary projections**
* Bilateral tumour
* The presence of ascites
* Extra-ovarian disease, including peritoneal thickening and omental deposits
* Increased vascularity by color Doppler.
* Irregular, multilocular, large mass > 10 cm

2. **Tumour markers**: CA125 is a non-specific tumour marker that is elevated in over 80% of epithelial ovarian cancers. It is only raised in approximately 50% of early-stage epithelial ovarian cancers and is also commonly raised in benign conditions such as pregnancy, endometriosis and alcoholic liver disease.

**The Risk of Malignancy Index (RMI)** is calculated from menopausal status, pelvic ultrasound features and CA125 level to triage pelvic masses into those at low, intermediate and high

RMI = U \* M \*CA125.

According to this patient are classified into:

1. Low risk : score < 25.
2. Moderate: score 25 -250.
3. High : score > 250.

Other tumour markers in Ovarian cancer management:



3.Pelvic pathology at intermediate or high risk of malignancy is further imaged using **computed tomography (CT)** and/or **magnetic resonance imaging (MRI)** scans.

The CT scan is particularly useful for assessment of extrapelvic disease and for staging. The MRI scan helps define tissue planes and operability.

4.Other investigations required for preoperative work-up include **chest X-ray**,

**electrocardiography (ECG)**, **full blood count, urea** and **electrolytes,** and **liver function tests.**

5.If the patient presents with gross ascites or pleural effusion, **paracentesis or pleural aspiration** may be required for symptom relief and/or diagnosis. A sample of the fluid removed is sent for cytological assessment.

6.If the diagnosis is uncertain or if primary chemotherapy is being considered (for advanced disease, or in patients not fit to undergo surgery), a **biopsy** is needed before treatment can be given. This is performed laparoscopically or radiologically (ultrasound or CT-guided biopsy). Usually the omentum is a good site for biopsy.

* **Staging**

Ovarian cancer staging is based on clinic-pathological assessment

 Overall, 25% of patients present with stage 1 disease, 10% stage 2, 50% stage 3 and 15% stage 4 disease.

### Stages of Ovarian Cancer

**Stage I: Ovarian cancer** is divided into three stages.

* Stage IA: Cancer is present in one ovary.
* Stage IB: Cancer is present in both ovaries.
* Stage IC: Cancer is present in one or both ovaries and cancer is found on the outside surface of one or both ovaries, or the outer covering of the tumor has ruptured, or cancer cells are found in the fluid or tissue linings of the abdomen.

**Stage II:**
In stage II ovarian cancer, cancer is present in one or both ovaries, and has spread to other parts of the **pelvic region**. There are three stages in stage II ovarian cancer.

* Stage IIA: Cancer has spread to the uterus and/or fallopian tubes.
* Stage IIB: Cancer is in one or both ovaries and has spread to other organs in the pelvic region such as the bladder, rectum, or sigmoid colon.
* Stage IIC: Cancer is found in one or both ovaries and has spread to the uterus, fallopian tubes, bladder, sigmoid colon, or rectum. Cancer may also be present is tissue and fluid samples of the lining of the abdominal cavity.

**Stage III**: In stage III ovarian cancer, cancer is found in one or both ovaries and has spread to the **abdomen**. Stage III ovarian cancer is divided into three different stages.

* Stage IIIA: Cancer is found in one or both ovaries and has spread to a small part of the abdomen.
* Stage IIIB: Cancer is present in one both ovaries and has spread to the peritoneum in an amount less than 2 centimeters. The peritoneum is the lining of the abdominal cavity.
* Stage IIIC: Cancer is found in one or both ovaries, and has spread to the peritoneum more than 2 centimeters and/or has spread to the lymph nodes.

**Stage IV**: Stage IV ovarian cancer is the most advanced stage of the disease. In this stage, cancer is found in one or both ovaries and has spread to parts of the body **beyond the abdomen**, like the **lungs** and **liver.**

**Metastatic spread:**

 2/3 of patient with ovarian cancer present with disease that has spread beyond the pelvis. Women with early ovarian cancer (stages 1 and 2) have up to 20% metastatic spread to lymph nodes and this rises to 60% in advanced disease

 1. Direct spread

 2. Peritoneal fluid (large& small bowel, parietal peritoneal surface, liver)

 3. Lymphatic spread (pelvic& para-aortic lymph nodes, cervical nodes)

 4. Haematogenous spread: usually occurs late (liver, lung, bone, brain).



* **Treatment**
1. **Surgery:**

 Provided the patient is fit to undergo anaesthesia, **surgery** remains necessary for: \***diagnosis**

 **\*staging**

 **\*treatment** of epithelial ovarian cancer.

If the patient is at high risk of ovarian cancer, the surgery should only be performed by a gynaecological oncologist, as this has been shown to improve outcomes.

The objective of surgery is to stage accurately the disease and remove all visible tumour. The aim of surgery is complete or optimal cytoreduction (where <1 cm of residual macroscopic disease is left behind).This is vitally important in ovarian cancer as many studies indicate that the most important prognostic factor is no residual disease following laparotomy.

**Principle of surgical treatment**:

* A vertical incision is required to gain access to all areas of the abdomen.
* Ascites or peritoneal washings are sampled
* A total abdominal hysterectomy and BSO performed along with an

omentectomy.

* Further debulking may be required, possibly including resection of bowel, peritoneal stripping or splenectomy in order to remove all tumour.
* Lymph node resection is important, particularly in early-stage disease
* Restaging can be offered after treatment and this may be carried out laparoscopically.
* Occasionally, young patients who are found to have an early-stage epithelial ovarian cancer wish to have conservative, **fertility sparing surgery**. In these cases, unilateral salpingo–oophorectomy, omentectomy, peritoneal biopsies and pelvic/para-aortic node dissection can be performed with endometrial sampling to exclude a synchronous tumour.

 **B.Chemotherapy**:

Chemotherapy can be given as **primary treatment**, as an **adjunct following surgery** or for **relapse of disease**.

 **Primary chemotherapy** may be offered if a patient is unfit or unwilling to have surgery, or if preoperative assessment indicates that complete debulking is unlikely to be achievable,. If the patient responds to the chemotherapy, interval surgery can be carried out after three cycles.

If the cancer has been properly staged as stage 1a or b, and is histologically low grade (well or moderately differentiated), chemotherapy may be withheld.

The role of chemotherapy in stage 1c disease is uncertain, but in practice most patients will be offered postoperative chemotherapy as with all other stages of epithelial ovarian cancer.

**Surgical management of ovarian cancer**

• Surgery combined with platinum-based chemotherapy is the mainstay of treatment for advanced ovarian cancer.

 **First-line treatment** is usually a combination of a platinum compound with paclitaxel. Most regimes are given on an outpatient basis, 3 weeks apart for six cycles.

* **Prognosis**

The survival figures depend on **stage at presentation**, **volume of disease** following surgery and the **histological grade** of tumour and **age** at resentation

The overall 5-year survival from ovarian cancer is 46% in the UK

Survival is stage dependent: overall 5-year survival for stage 1 disease is over 90% compared to 30% for stage 3 disease.

**Primary peritoneal carcinoma**

* **Sex cord stromal tumours**:

These tumours account for approximately 10% per cent of ovarian tumours, but almost 90% cent of all **functional (i.e. hormone-producing)** tumours.

Generally, they are tumours of low malignant potential with a good long-term prognosis.

Some morbidity may arise from the oestrogen (granulosa cell) or androgen production (Seroli–Leydig cell) characteristic of these tumours, resulting in **precocious puberty**, **abnormal menstrual bleeding** and an increased risk of **endometrial cancer**.

The peak incidence is around the age of the menopause

Sertoli–Leydig cell tumours produce androgens in over 50% of cases. Patients present with a pelvic mass and signs of virilization. Common symptoms are amenorrhoea, deep voice and hirsutism Occasionally, this group of tumours produce oestrogen and rarely renin, causing hypertension.

Granulosa cell tumours produce inhibin, which can be used for follow-up

**Treatment**

 Surgery is the mainstay of treatment as there is no effective chemotherapy regime.

**Germ cell**

* **Germ cell tumours**

Malignant germ cell tumours occur mainly in young women and account for approximately 10% of ovarian tumours.

They are derived from primordial germ cells within the ovary and because of this may

contain any cell type.

**Dysgerminomas** account for 50% of all germ cell tumours. They are bilateral in 20% of cases and occasionally secrete human chorionic gonadotrophin **(hCG).**

**Endodermal sinus yolk sac** tumours are the second most common germ cell tumours They are rarely bilateral and secrete α-fetoprotein **(AFP**).

**Immature teratomas** are malignant germ cell tumours and about 1% of all

teratomas. They are classified as mature or immature depending on the grading of neural tissue present. About one-third of teratomas secrete **AFP**.

**Non-gestational choriocarcinomas** are very rare, usually presenting in young girls with irregular bleeding and very high levels of **hCG**.

**Treatment**

As most women presenting with malignant germ cell tumours are of

reproductive age, fertility-sparing surgery is the mainstay with chemotherapy if the disease reaches outside the ovary.

The most common regime used is a combination of bleomycin, etoposide and cisplatin (BEP). This regime preserves fertility

References:

Gynecology by ten teachers

Dewhurt's textbook of Obstetrics and gynecology**Further reading**

Barakat RR, Bevers MW, Gershenson DM, Hoskins WJ (eds) (2002). *Handbook of Gynecologic Oncology*.

End of lecture