1 Histopathology of gynaecological cancers

Ovarian tumours

Ovarian tumours are classified based on cell types, patterns of growth and, whenever possible, on histogenesis (WHO Classification 2014).

There are 3 major categories of primary ovarian tumour: epithelial tumours (ETs), sex cord–stromal tumours (SCSTs) and germ cell tumours (GCTs). Secondary tumours are not infrequent.

The incidence of malignant forms varies with age. Carcinomas, accounting for over 80%, peak at the 6th decade; SCSTs peak in the perimenopausal period; GCTs peak in the first three decades. Prognosis is worse for carcinomas.

Classification of Tumours of the Ovary
Epithelial tumours (ET)
Sex cord–stromal tumours (SCST)
Germ cell tumours (GCT)
Monodermal teratoma and somatic type tumours arising from dermoid cyst
Germ cell–sex cord stromal tumours
Mesenchymal and mixed epithelial and mesenchymal tumours
Other rare tumours, tumour-like conditions
Lymphoid and myeloid tumours
Secondary tumours

WHO, 2014

Stage I: Tumour confined to ovaries or Fallopian tube(s)
IA: Tumour limited to 1 ovary (capsule intact) or Fallopian tube; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB: Tumour limited to both ovaries (capsules intact) or Fallopian tubes; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC: Tumour limited to 1 or both ovaries or Fallopian tubes, with any of the following: • **IC1:** Surgical spill • **IC2:** Capsule ruptured before surgery or tumour on ovarian or Fallopian tube surface • **IC3:** Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves 1 or both ovaries or Fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA: Extension and/or implants on uterus and/or Fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal tissues

FIGO, 2013

The staging classification has been recently revised (FIGO 2013 Classification) and ovarian, Fallopian tube and peritoneal cancer are classified together.

Stage I cancer is confined to the ovaries or Fallopian tubes. Peritoneal cytology/washing, tumour rupture or surface involvement warrants a Stage IC.

In Stage II, the disease involves one or both ovaries/ Fallopian tubes with extension to the pelvis below the pelvic brim (note: peritoneal cancer has no FIGO Stage I).

Most patients with ETs present at high stage (III-IV). In Stage III, the disease involves one or both adnexae and spread to the pelvic and abdominal peritoneum and/or retroperitoneal lymph nodes.

Stage IV includes patients with pleural diffusion and intraparenchymal liver/spleen or extra-abdominal metastases or extra-abdominal lymph nodes (LNs).

The revised FIGO staging system better reflects the prognosis of patients with ovarian cancer and LN metastases.

Stage III: Tumour involves 1 or both ovaries or Fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1: Positive retroperitoneal lymph nodes only • **IIIA1(i)** Metastasis up to 10 mm • **IIIA1(ii)** Metastasis more than 10 mm
IIIA2: Microscopic extrapelvic peritoneal involvement with or without positive lymph nodes
IIIB: Macroscopic extrapelvic peritoneal metastasis up to 2 cm, with or without metastasis to the retroperitoneal lymph nodes
IIIC: Extrapelvic peritoneal metastasis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
Stage IV: Distant metastasis excluding peritoneal metastases
IVA: Pleural effusion with positive cytology
IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO, 2013

REVISION QUESTIONS

1. How many categories of ovarian tumour can be classified?
2. If the disease is on the bladder peritoneum, is the patient staged as Stage IIA or IIB?
3. If the disease involves the abdominal peritoneum and mediastinal LNs, is the patient staged as Stage IIIC or IVB?

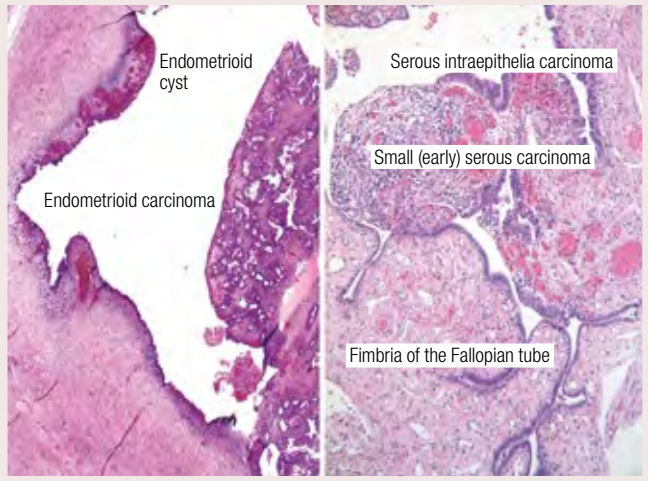
Epithelial ovarian tumours

Primary ETs are classified based on histological type and into benign, borderline (atypical, non-invasive) and malignant. Carcinomas represent a heterogeneous group of different diseases.

Some carcinomas follow a benign–adenoma–carcinoma morphological and molecular pathway in the ovary: they are frequently unilateral, low grade (in most cases), and show lower levels of genetic anomalies. Staging is prognostically relevant.

High-grade serous carcinomas are usually detected at high stage and no macroscopic residual disease after debulking is the main prognostic variable. All show *p53* mutations and genetic instability; *BRCA* genes are involved in hereditary and in some sporadic cases.

Site of origin (+ immunohistochemical markers) and histological type (+ *genetic association*) of ovarian carcinomas
Fallopian tube (PAX8, WT1) High-grade serous (*p53, BRCA1, BRCA2*)
Endosalpingiosis, serous borderline tumours (PAX8, WT1) Low-grade serous (*BRAF, Kras, PIK3CA, MSI*)
Endometriosis (PAX8, ER, PR) Clear cell (*ARID1a*) Endometrioid (*ARID1a, β-catenin, PTEN, MSI*)
Not known, tubal peritoneal-junction? (-) Mucinous (*Kras, HER2*) Brenner



Endometrioid and clear cell carcinomas may arise in endometriosis. Borderline tumours are rare and clinically benign, but can be found associated with carcinomas. Grading is relevant in endometrioid carcinomas.

Mucinous carcinomas usually develop within borderline tumours (otherwise clinically benign) and behaviour is dependent on the presence of invasion and high grade of atypia.

Serous borderline tumours can develop from inclusion cysts. They can present as Stage >1 and may recur. Invasive peritoneal implants are markers for progression and represent evolution into low-grade serous carcinoma, which may also develop in the ovary and peritoneum.

High-grade serous carcinomas are the most frequent carcinomas. Unlike previously thought, they often do not arise in the ovary. The distal Fallopian tube is the site of origin in BRCA patients and it is commonly involved in sporadic cases. Serous intraepithelial carcinoma (STIC) is considered the precursor lesion; however, it can already metastasise.

Ovarian Carcinomas			
Type	**%**	**Stage 1 %**	**Survival %**
Type 1			
Endometrioid	10	>60	78
Clear cell	10	>60	80
Mucinous	3	80	80
Low-grade serous	<5		>85
Type 2			
High-grade serous	70	<5	40

REVISION QUESTIONS

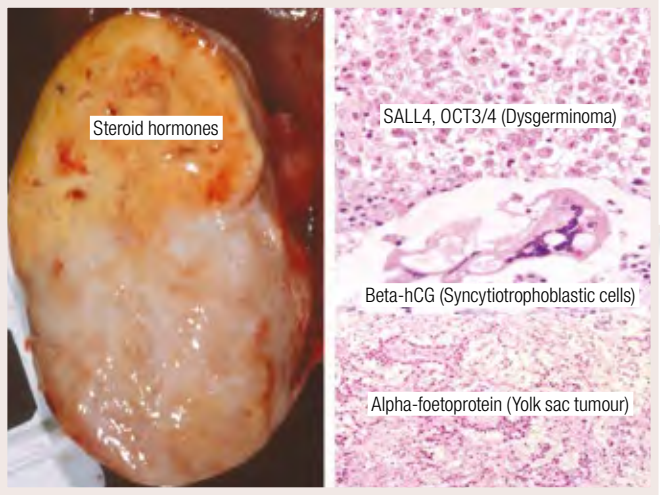
1. What is the most frequent and more frequently disseminated type of ovarian carcinoma?
2. What are the most important prognostic variables in serous carcinomas?
3. What is considered the main precursor of clear cell carcinoma of the ovary?

Non-epithelial ovarian tumours

Non-epithelial tumours are typically unilateral. Those that contain granulosa cells and Sertoli cells ("sex cords"), theca cells, fibroblasts, Leydig cells and steroid cells not otherwise specified form a broad category of rare tumours characterised by endocrine manifestations (SCSTs).

Granulosa cell tumours are low-grade malignant tumours with late recurrence. Most occur in adults; the rare juvenile type is aggressive when ruptured. Grading has value in Sertoli cell tumours.

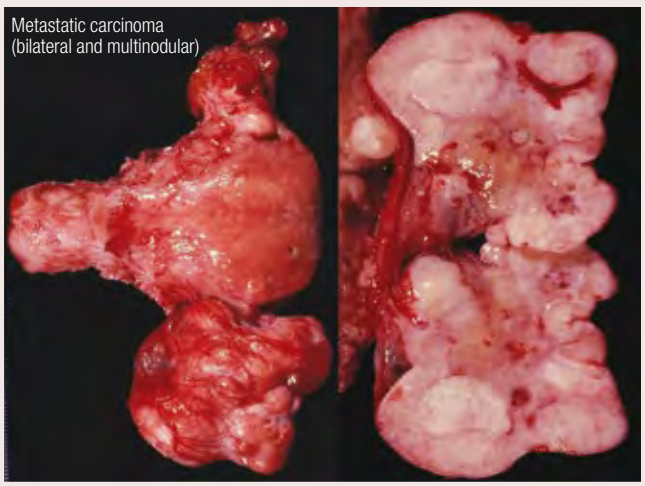
Steroid cell tumours can be malignant. Staging is prognostically relevant for all of these. The other tumours are benign.



Most GCTs are benign mature teratomas (dermoid cysts); only rarely may a malignant tumour arise from somatic-type teratomatous tissues. Primitive (malignant) GCTs are similar to those occurring in males; a few occur in subjects with disorders of sexual development (most phenotypically females with Y chromosome) from a mixed germ cell–sex cord stromal tumour (gonadoblastoma).

Primitive GCTs include dysgerminoma (similar to seminoma), yolk sac tumour and rarer types (embryonal carcinoma and choriocarcinoma) alone or in combination (10%). Immature (embryonal) teratomas also are in this group. Tumour cell markers and chemosensitivity are typical.

Among undifferentiated cancers, some mimic undifferentiated carcinomas of other organs (lung); one aggressive type associated with hypercalcaemia typically arises in the first decades.



Metastatic tumours from the gastrointestinal tract may simulate primary mucinous carcinomas. Those from the stomach and breast show typical features, bilaterally and single-cell growth alone or with other features.

Tumour-like lesions may simulate malignant tumours.

REVISION QUESTIONS

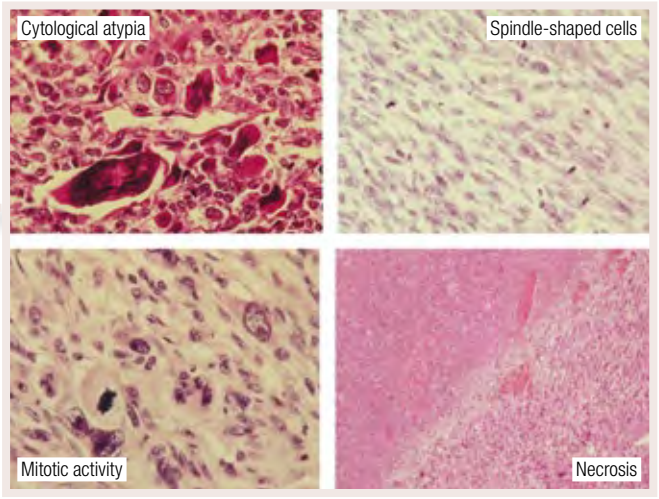
1. What is the most important prognostic histological feature in malignant SCSTs?
2. Why is the prognosis of malignant primitive germ cell tumours favourable in most cases?
3. Are bilateral mucinous (intestinal-type) carcinomas most likely to be primary or metastatic?

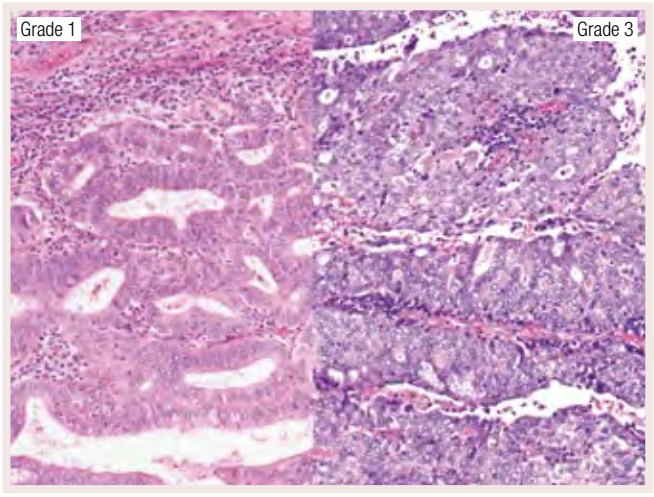
Uterine corpus tumours

In the uterine corpus there are three major categories of cancer: (1) epithelial, (2) mesenchymal and (3) mixed epithelial and mesenchymal.

Uterine leiomyosarcoma (LMS) is the most common type of mesenchymal malignant tumour; microscopic features of LMS include cytological atypia, mitotic activity and necrosis. They are aggressive also when Stage 1.

Endometrial stromal sarcoma is less frequent than LMS. Most are low-grade tumours and the stage is prognostically relevant; few are high grade. They show typical genetic anomalies.





FIGO staging of endometrial carcinoma: Stage I: limited to the corpus; Stage II: infiltration of the cervical stroma; Stage III: metastases to adnexa, vagina and retroperitoneum; and Stage IV: metastases to bladder, rectum and distant organs.

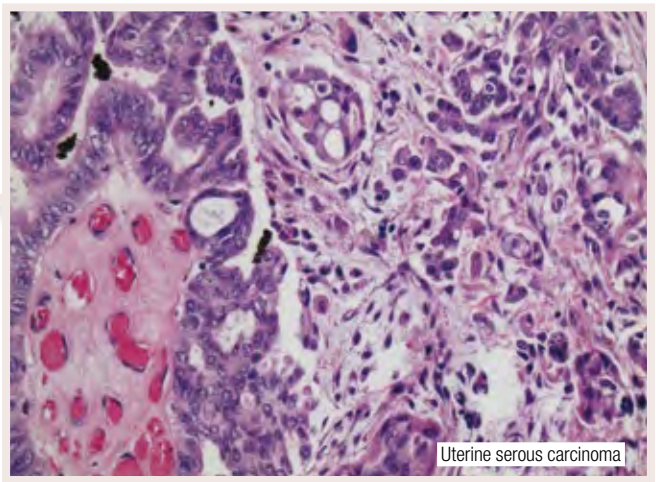
There are two stereotypes of endometrial carcinoma. Type 1 (75%), or low-grade endometrioid carcinomas, present at low stage in perimenopause and are associated with unopposed oestrogen stimulation, obesity and infertility. Prognosis depends on depth of myometrial invasion and stage. Grading is mixed, architectural and nuclear. Molecular changes include microsatellite instability, mutations of *p-TEN*, *k-RAS*, and *β-catenin*.

Type 2 (10%), or serous carcinoma, arises in atrophic endometrium in postmenopausal women and is more aggressive. *p53* mutations and genetic instability are characteristic.

A third minor type, clear cell carcinoma, shows intermediate features.

An integrated genomic characterisation of endometrial carcinoma identified four different prognostic subgroups: *POLE* ultramutated, microsatellite instability hypermutated, copy number low and copy number high.

This may impact postsurgical treatments for aggressive tumours.



REVISION QUESTIONS

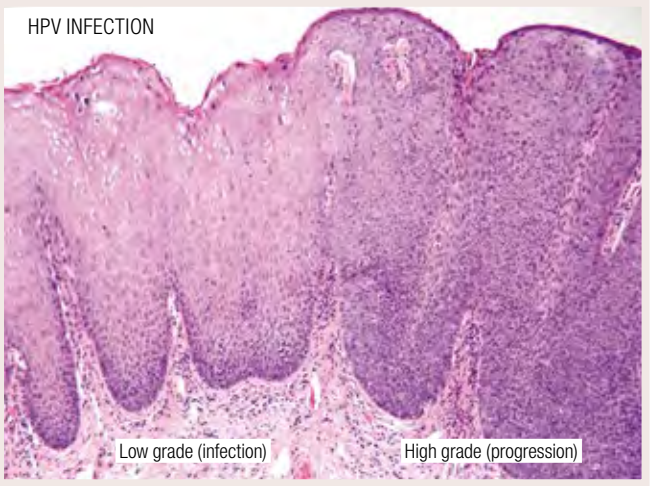
1. What are the diagnostic histological features of uterine LMS?
2. What are the clinical features of Type 1 and Type 2 endometrial carcinomas?
3. What are the molecular features of Type 1 and Type 2 endometrial carcinomas?

Uterine cervical tumours

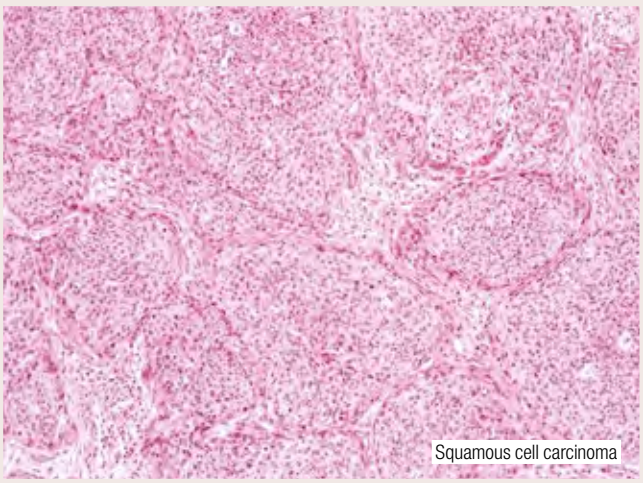
Cervical cancer is the most serious complication of human papillomavirus (HPV) infection, particularly from some HPV types designated as "high-risk HPV" (mostly Types 16 and 18).

Two viral reading frames, E6/E7, deregulate reparative proteins, p53 and Rb, at cell cycle check points favouring genetic errors and malignant transformation.

The declining incidence of cervical cancer over the last decades is related to screening programmes that detect early cancers or precursor lesions. Vaccination is a new horizon for prevention.



HPV, Human papillomavirus.



FIGO staging: Stage I: limited to the cervix; Stage II: initial parametria/vagina; Stage III: deep infiltration parametria/vagina; Stage IV: bladder/rectum/distant metastasis.

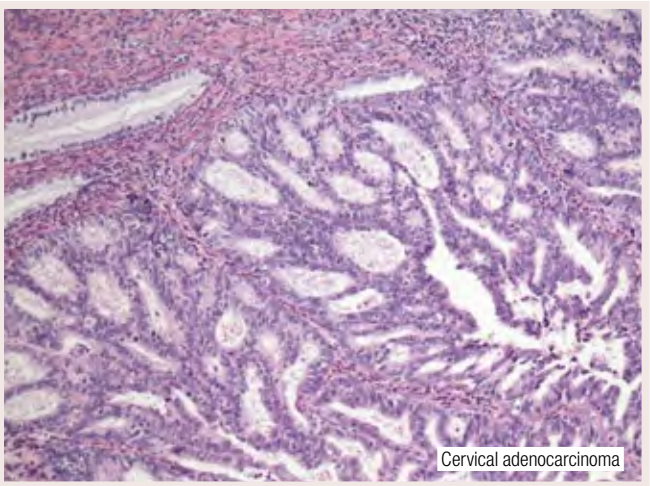
Squamous cell carcinoma accounts for 70% of cervical cancers. Pre-invasive lesion (cervical intraepithelial neoplasia, CIN) features include well-known condylomatous changes or low-grade CINs (multinucleation and perinuclear halos) and features suggestive of malignancy or high-grade CINs (marked cell atypia, and p16 positivity).

Invasive carcinoma is usually of the non-keratinising type.

Adenocarcinomas account for 20%–25% of cervical cancers and are difficult to detect by screening. Most are HPV cancers and HPV18 is frequent. Histological types include endocervical and mucinous; mixed adenosquamous carcinomas may occur.

Small cell undifferentiated carcinoma is the least frequent, but a highly aggressive, HPV cancer.

A few adenocarcinomas are not HPV related; they include gastric type mucinous and clear cell adenocarcinoma and adenocarcinoma arising from mesonephric remnants.



REVISION QUESTIONS

1. Why is the incidence of cervical cancer in developed countries decreasing? What is a promising discovery for reducing cervical cancer incidence even in developing countries?
2. What are the most common, high-risk HPVs related to invasive cervical cancer? What is the molecular pathogenesis?
3. What HPV-related features can be identified at cytology/histology?

Summary: Histopathology of gynaecological cancers

- Ovarian tumours:
  - Epithelial ovarian tumours
  - Sex cord ovarian tumours
  - Germ cell ovarian carcinomas
- Ovarian cancer is not a homogeneous disease, but rather a group of diseases—each with different morphology and biological behaviour. Reproducible histopathological diagnosis of tumour cell type is a conditio sine qua non for successful treatment. FIGO staging has recently been revised and reflects the tumour dissemination and subsequent prognosis
- Uterine corpus tumours:
  - Sarcomas
  - Type 1: Endometrioid carcinomas
  - Type 2: Serous carcinomas
- In uterine corpus cancers, three major types can be identified according to their intrinsic biology and subsequent treatments: (1) epithelial, (2) mesenchymal and (3) mixed epithelial and mesenchymal
- Uterine cervical tumours:
  - HPV and pre-invasive lesions
  - Squamous carcinoma
  - Adenocarcinomas
- Cervical cancers mainly derive from high-risk HPV infections (mostly by HPV16/18). Here we describe the pathological features of the two principal subtypes: (1) squamous cell carcinoma, (2) adenocarcinomas

Further Reading

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