1 Histopathology of gynaecological cancers

Tubo-ovarian tumours – Classification and germ cell tumours (GCTs)

Classification: female adnexal tumours consist of epithelial tumours (most common), sex cord-stromal tumours (SCSTs) and GCTs, as well as metastases.

Tumours are further classified as benign, low-grade malignant or fully malignant, with the majority of the latter being epithelial (carcinomas).

Ovarian cancer is a heterogeneous group of tumours; globally, it ranks eighth in terms of incidence and mortality among women.

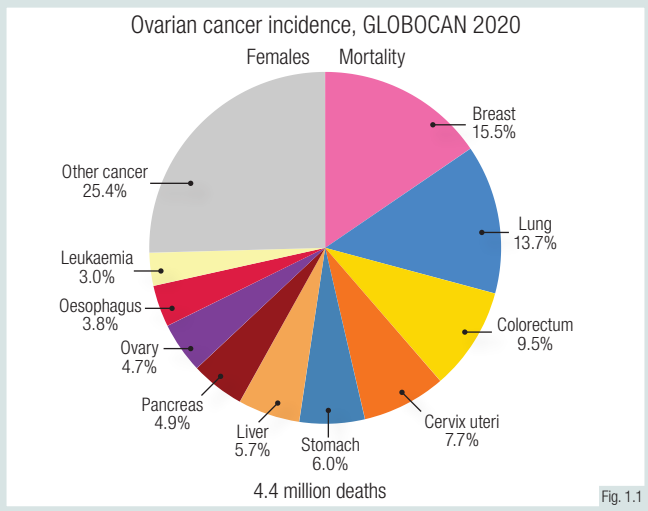


Fig. 1.1

Mature teratoma

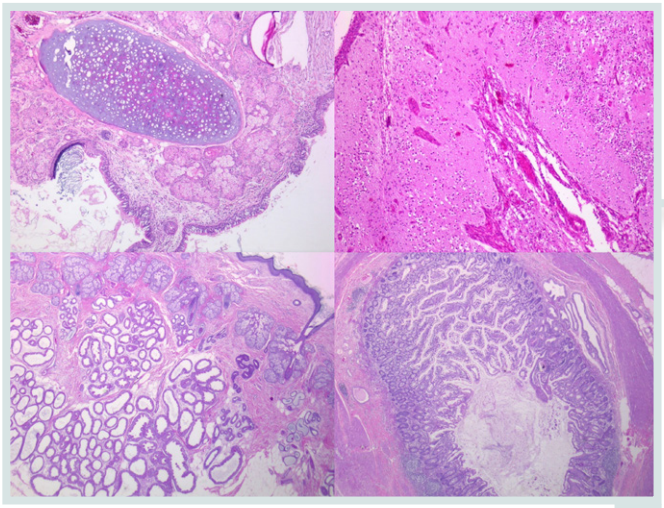


Fig. 1.2

The majority of GCTs are unilateral tumours diagnosed in young women. The most common is mature teratoma, which accounts for 20% of ovarian tumours.

Mature teratomas often contain all three germ layers, though monodermal forms exist, e.g. *struma ovarii*, which consists of thyroid tissue.

Mature teratomas should be adequately sampled to rule out an immature component or malignant tumour of somatic type.

Malignant GCTs consist of dysgerminoma, yolk sac tumour, immature teratoma, embryonal carcinoma and choriocarcinoma, or mixed forms.

Immunostains used in diagnosis include stem cell markers (SOX2, SALL4, OCT3/4), alpha-foetoprotein (AFP), human chorionic gonadotropin (hCG) and c-Kit.

Chromosome 12 abnormalities and *KIT* mutation or amplification are seen in dysgerminoma but are not used in the diagnostic setting.

Immature teratoma and dysgerminoma

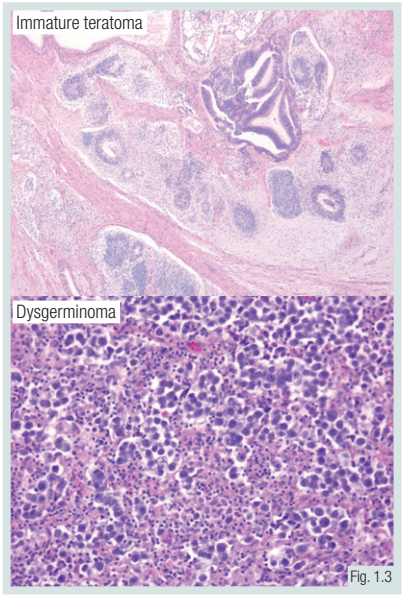


Fig. 1.3

REVISION QUESTIONS

1. How are female adnexal tumours classified?
2. Are the majority of GCTs in females benign or malignant?
3. What types of malignant GCT are recognised?

Tubo-ovarian tumours – SCSTs

SCSTs are typically unilateral tumours and often hormonally active; the most common type is fibroma, which is benign.

A minority of tumours, granulosa cell tumours and Sertoli–Leydig cell tumours, may be malignant, and may recur many years after oophorectomy.

Tumours are often hormonally active, causing endometrial neoplasia when oestrogens predominate and masculinisation when androgens predominate.

Metastasis from adult granulosa cell tumour

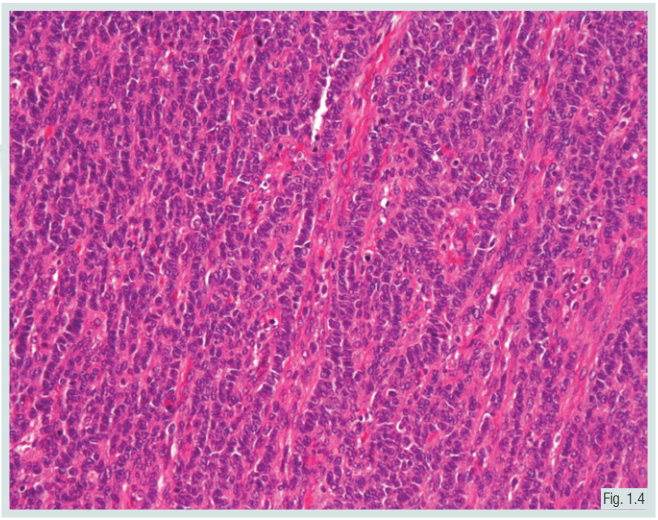
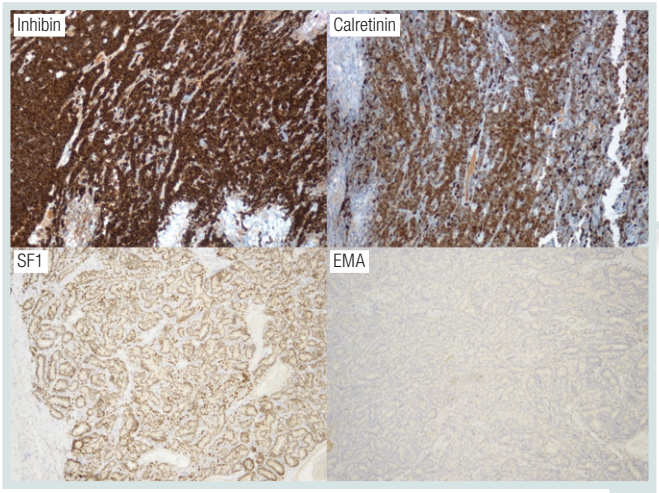


Fig. 1.4

Immunostaining of granulosa cell tumour, adult type



EMA, epithelial membrane antigen; SF1, steroidogenic factor-1.

Fig. 1.5

Granulosa cell tumours are classified as adult (more common, present in peri-/postmenopausal women) or juvenile (rare, present in first 4 decades); they have different hormonal manifestations.

Tumours stain for inhibin, steroidogenic factor-1 (SF1), FOXL2 and calretinin, and are negative for epithelial membrane antigen.

Point mutation in *FOXL2* is characteristic of tumours of the adult type, and can aid diagnosis in challenging cases.

Sertoli–Leydig cell tumours

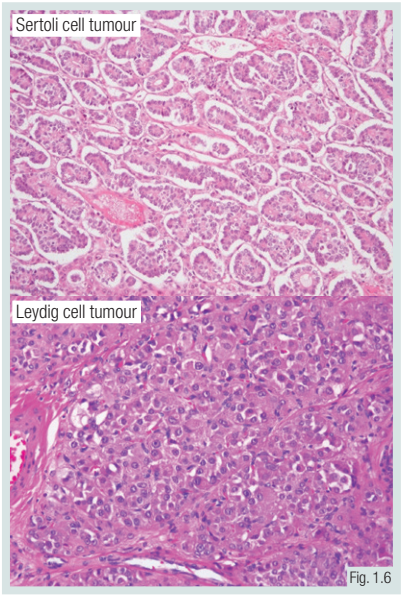


Fig. 1.6

Sertoli–Leydig cell tumours have a wide age range at presentation. They can occur as either a combined tumour or be composed solely of Sertoli or Leydig cells.

Sertoli tumours are morphologically heterogeneous, may contain heterologous elements, and are graded well, moderate or poorly differentiated, indicating increasing aggressiveness.

Tumours express sex cord-stromal immunomarkers and may carry mutations in *DICER1* or *FOXL2* genes.

REVISION QUESTIONS

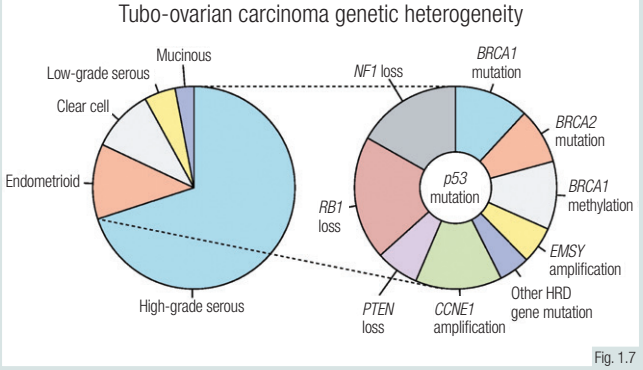
1. Are the majority of SCSTs benign or malignant?
2. What are the useful diagnostic stains for SCSTs?
3. Are there any genetic tests used to classify these tumours?

Tubo-ovarian tumours – Epithelial tumours

Tubo-ovarian carcinomas consist of high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), clear cell carcinoma (CCC), endometrioid ovarian carcinoma (EOC) and mucinous carcinoma (MC).

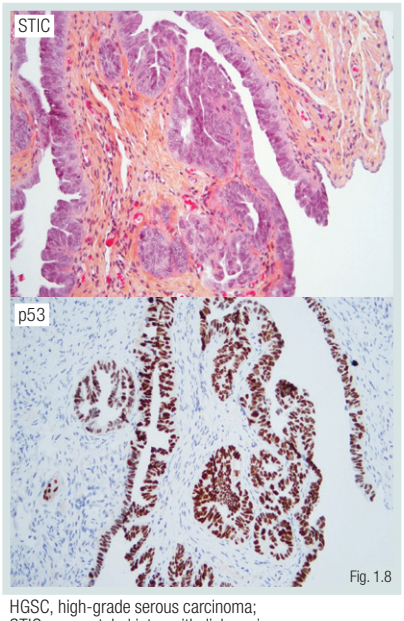
These five histotypes are five different diseases, each with its own pathogenesis, morphology, immunohistochemistry (IHC) profile, genetic features, prognosis and clinical response to chemotherapy (ChT) and targeted therapy.

Borderline tumours are tumours of low malignant potential that can be precursors of LGSC, CCC, EOC and MC, often carrying mutations related to the corresponding carcinoma.



HRD, homologous recombination deficiency; NF1, neurofibromin 1; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma 1.

STIC and HGSC



HGSC, high-grade serous carcinoma;
STIC, serous tubal intraepithelial carcinoma.

HGSC is the most common extra-uterine carcinoma histotype (70%); the majority develop from serous tubal intraepithelial carcinoma (STIC) in the fimbrial region, and harbour universal *TP53* mutations, *BRCA1/2* mutations in 15%–30% of cases.

The majority express the female genital marker PAX8 and the serous marker WT1, and have an aberrant (diffusely positive, entirely negative or cytoplasmic) p53 staining pattern.

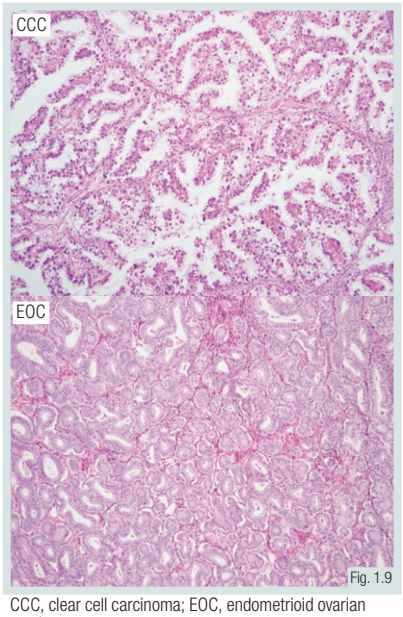
It is a clinically aggressive tumour often diagnosed at an advanced stage. Debulking to no macroscopic disease, ChT and PARP (poly [ADP-ribose] polymerase) inhibition are mainstays of therapy.

Other histotypes: LGSCs develop from serous borderline tumours, stain for PAX8 and WT1, have wild-type p53 and are characterised by *KRAS/NRAS/BRAF* mutation.

EOC and CCC are endometriosis-associated tumours harbouring mutations in phosphatase and tensin homologue (*PTEN*) and *CTNNB1* (mainly EOC) and *ARID1A* and *PIK3CA* (both); hepatocyte nuclear factor 1 beta (*HNF1β*) is often overexpressed; both are PAX8-positive.

MCs develop from mucinous borderline tumours or mature teratomas, have an expansile (indolent) or infiltrative (aggressive) pattern and harbour *KRAS* and *TP53* mutations and *ERBB2* amplification.

EOC and CCC



CCC, clear cell carcinoma; EOC, endometrioid ovarian carcinoma.

REVISION QUESTIONS

1. What are the five tubo-ovarian carcinoma histotypes?
2. What is the name of the preinvasive lesion from which HGSC develops?
3. Which carcinomas are associated with endometriosis?

Uterine corpus tumours – Epithelial tumours

The majority of malignant uterine corpus tumours are carcinomas, which are classified as endometrioid, serous, clear cell, mixed type or other, rarer subtypes.

Endometrial cancers (ECs) are broadly divided into oestrogen-dependent (endometrioid) and oestrogen-independent (non-endometrioid), though mixed and hybrid forms exist.

The most common predisposing genetic condition for developing EC is Lynch syndrome, in which mutations occur in mismatch repair (MMR) genes.

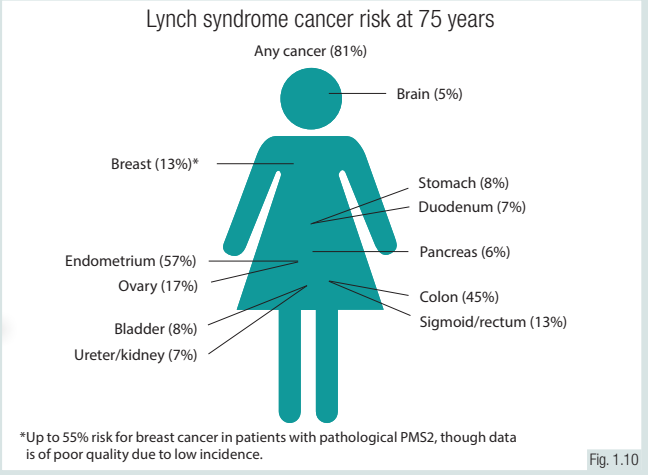


Fig. 1.10

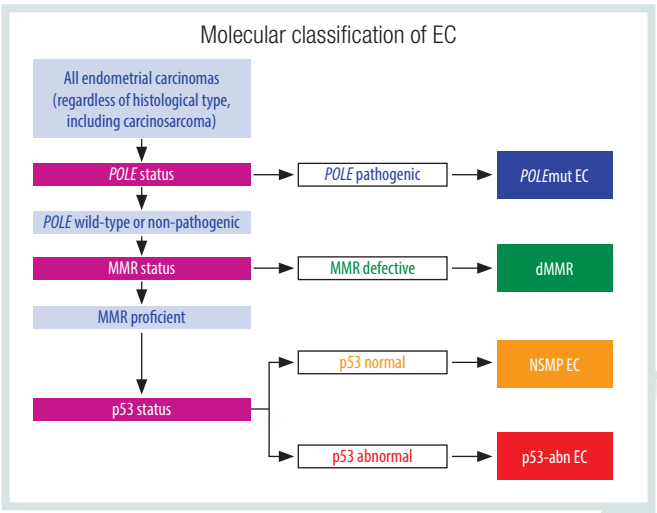


Fig. 1.11

dMMR, MMR-deficient; EC, endometrial cancer; MMR, mismatch repair; NSMP, no specific molecular profile; p53-abn, p53 abnormal; POLE, polymerase epsilon; POLEmut, POLE ultramutated.

Endometrioid endometrial carcinoma (EEC) is the only EC histotype that is graded. Low-grade tumours generally have good prognosis and high-grade tumours often behave aggressively.

EEC has frequent loss of the *PTEN* tumour suppressor and often expresses hormone receptors, whereas aberrant p53 and diffuse p16 staining pattern is associated with clinically aggressive tumours.

The Cancer Genome Atlas (TCGA) classification is central to molecular risk assessment in EEC and other histotypes, with a surrogate test based on p53, MMR IHC and *POLE* (polymerase epsilon) mutation analysis.

Other histotypes: Serous carcinomas are aggressive tumours characterised by *TP53* mutations; serous endometrial intraepithelial carcinoma (SEIC) is a preinvasive precursor.

CCCs are rare when diagnosed based on strict criteria, often carry *ARID1A* mutations, overexpress HNF1β and are hormone receptor-negative.

Rare EC histotypes include carcinosarcoma, mesonephric-like carcinoma, mucinous carcinoma of intestinal type and squamous cell carcinoma (SCC).

Serous carcinoma

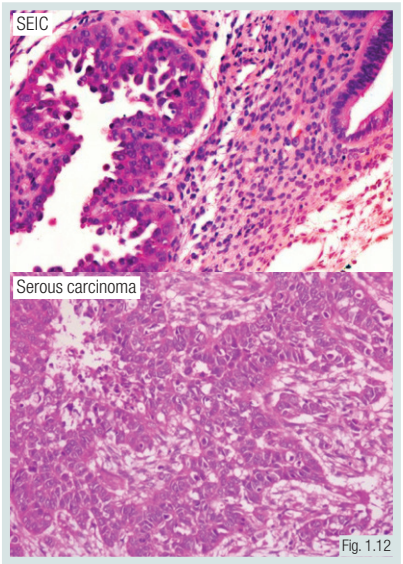


Fig. 1.12

SEIC, serous endometrial intraepithelial carcinoma.

REVISION QUESTIONS

1. Which genetic syndrome is associated with increased risk for developing EC?
2. Which ancillary tests are applied to the molecular classification of EC?
3. What is the precursor of uterine serous carcinoma?

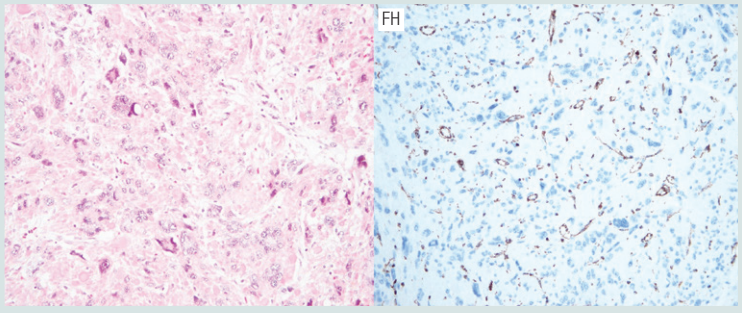
Uterine corpus tumours – Non-epithelial tumours

The majority of non-epithelial tumours affecting the uterine corpus are mesenchymal, including the very common leiomyoma, and rare uterine sarcomas (3% of uterine malignancies).

The most common uterine sarcoma is leiomyosarcoma (LMS), followed by endometrial stromal sarcoma (ESS), the latter divided into low- and high-grade entities (LG-ESS, HG-ESS).

Leiomyomas are clonal, morphologically heterogeneous, and often harbour *MED12* mutations, whereas leiomyomas with bizarre nuclei may be associated with fumarate hydratase (FH) deficiency.

Leiomyoma with FH deficiency



FH, fumarate hydratase.

Fig. 1.13

Gene fusions in ESS

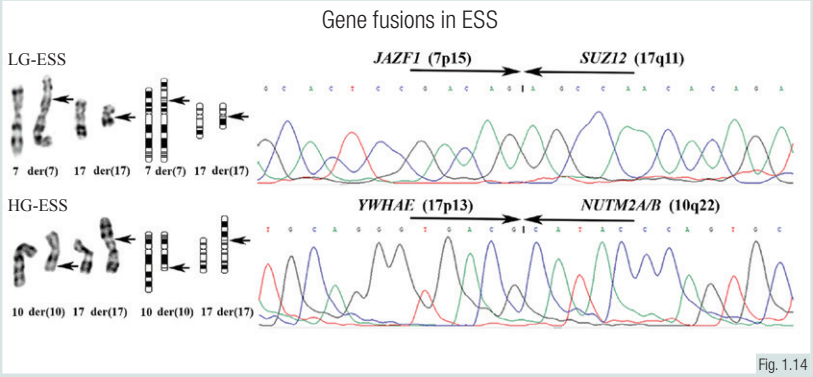


Fig. 1.14

ESS, endometrial stromal sarcoma; HG, high-grade; LG, low-grade.

Uterine sarcomas: LMSs are clinically aggressive tumours, stain for muscle markers (desmin, actin, caldesmon), and may harbour mutations in *TP53*, *ATRX* and *MED12*.

LG-ESS express CD10 and hormone receptors, whereas HG-ESS are often negative for these markers and show overexpression of cyclin D1 or BCOR.

LG-ESS carry different fusion genes, most commonly *JAZF1-SUZ12*, whereas HG-ESS have *YWHAE-NUTM2A/B* fusion or fusions involving *BCOR*.

Gestational trophoblastic disease (GTD) includes tumour-like conditions, molar pregnancies (partial, complete or invasive mole) and gestational trophoblastic neoplasia (GTN).

Complete mole carries a 15%–20% risk for persistent disease and a 2%–3% risk of developing choriocarcinoma, the most common and clinically aggressive GTN.

The diagnosis of molar pregnancy is based on p57 immunostaining and DNA content, the latter by genetic typing.

WHO 2020 classification of gestational trophoblastic disease (GTD)

Tumour-like lesions
Exaggerated placental site reaction
Placental site nodule and plaque
Molar pregnancies
Partial hydatidiform mole
Complete hydatidiform mole
Invasive and metastatic hydatidiform moles
Gestational trophoblastic neoplasms
Epithelioid trophoblastic tumour (ETT)
Placental site trophoblastic tumour (PSTT)
Gestational choriocarcinoma
Mixed trophoblastic tumour

Fig. 1.15

WHO, World Health Organization.

REVISION QUESTIONS

1. Which types of sarcomas are most common in the uterus?
2. Which type of genetic change is characteristic of ESS?
3. Which ancillary tests are used in the diagnosis of molar pregnancy?

Uterine cervix tumours

Cervical neoplasia pertains primarily to epithelial tumours, including SCC, adenocarcinoma and neuroendocrine carcinoma; other entities are rare.

Glandular precursors and invasive tumours are divided into human papillomavirus (HPV)-associated and HPV-independent entities; squamous tumours are almost universally HPV-associated.

Immunostaining for p16 is a surrogate marker of HPV infection, although there is not full concordance between HPV molecular typing and p16 staining.

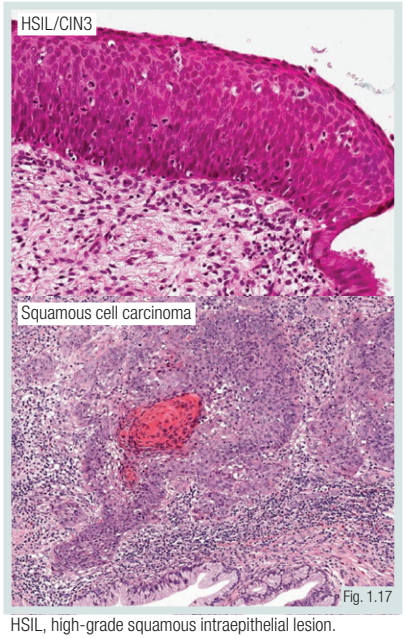
WHO 2014 and IECC 2018 classifications of cervical adenocarcinomas*

WHO 2014	IECC 2018	
Usual type	HPV-associated (HPVA)	Non-HPV-associated (NHPVA)
Mucinous carcinoma, NOS	Usual type	Gastric type
Gastric type	Villoglandular	Clear cell
Intestinal type	Mucinous, NOS	Mesonephric
Signet ring cell	Mucinous, intestinal	Endometrioid
Villoglandular	Invasive stratified mucin-producing	
Endometrioid	Micropapillary	
Clear cell	'Serous'-like	
Serous		
Mesonephric		Fig. 1.16

*The 5th edition of the WHO Classification of Female Genital Tumours (2020) has incorporated the 2018 IECC system for endocervical adenocarcinomas, as well as the Silva pattern-based classification.

HPV, human papillomavirus; IECC, International Endocervical Adenocarcinoma Criteria and Classification; NOS, not otherwise specified; WHO, World Health Organization.

HSIL/CIN3 and invasive squamous cell carcinoma



HSIL, high-grade squamous intraepithelial lesion.

Squamous cell neoplasia: low- and high-grade squamous intraepithelial lesions (LSIL, HSIL) are precursors of SCC; the latter is associated with a higher risk of progression.

HPV16 is the most commonly found virus type, and is associated with the highest risk of transformation, occurring via integration of the *E6* and *E7* viral genes and deactivation of p53 and retinoblastoma (Rb), respectively.

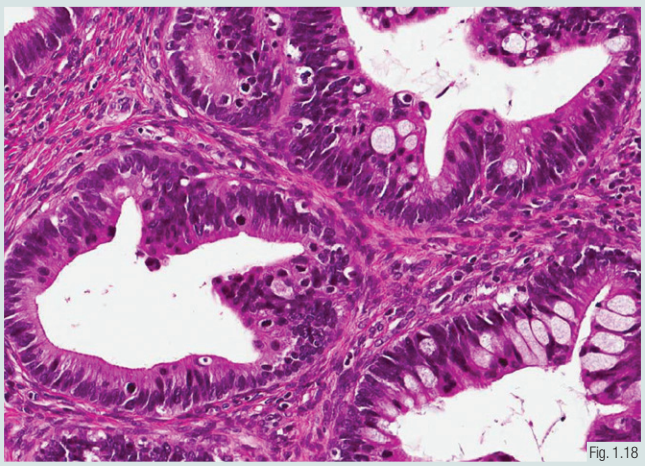
The majority of SCCs are focally- or non-keratinising; grading is not informative of prognosis.

Columnar cell neoplasia: HPV-associated adenocarcinomas constitute 80% of cervical adenocarcinomas and develop from adenocarcinoma *in situ* (AIS); HPV16 and HPV18 are the most commonly found virus types.

A grading of HPV-associated adenocarcinoma based on architecture and stromal response (the Silva classification) has been proposed.

The most common HPV-independent adenocarcinoma is of gastric type; these tumours often have aberrant p53 staining and worse stage-matched prognosis compared with HPV-associated tumours.

HPV-associated adenocarcinoma



HPV, human papillomavirus.

REVISION QUESTIONS

1. Which malignant tumours are most common in the cervix?
2. Which tumours are classified based on HPV status?
3. What type of HPV-independent adenocarcinoma is the most common?

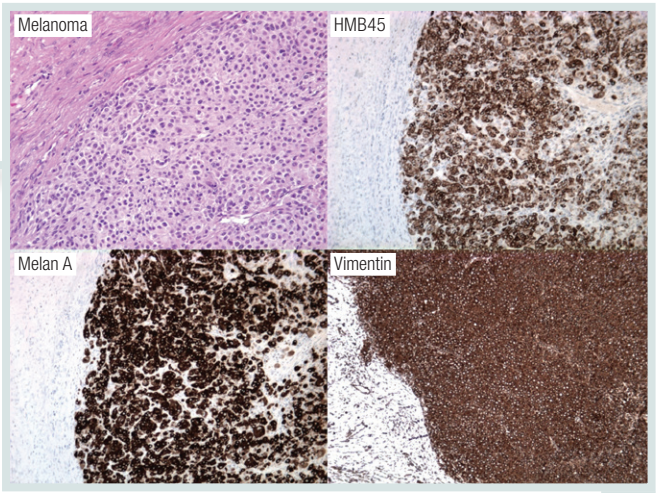
Vulvar tumours

The majority of vulvar cancers are squamous cell carcinomas (VSCCs), which are divided into HPV-associated and HPV-independent tumours.

Other entities diagnosed at this location include Paget disease, invasive adenocarcinoma, basal cell carcinoma, melanoma, adnexal tumours, mesenchymal tumours and metastases.

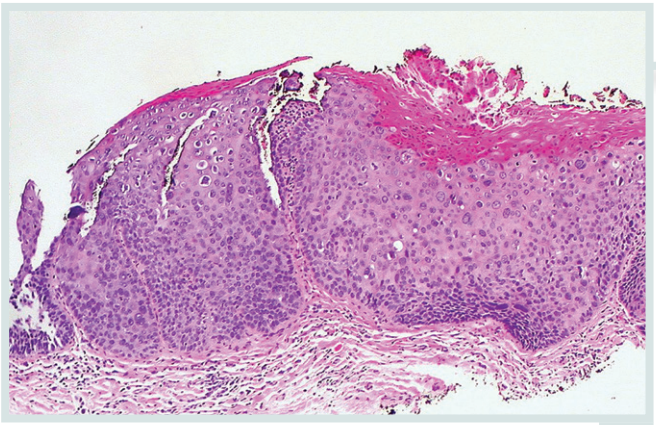
Immunostaining for p16 is a surrogate marker of HPV infection, although there is not full concordance between HPV infection and p16 staining.

Vulvar melanoma; H&E staining and expression of HMB45, Melan A and vimentin



H&E, haematoxylin and eosin. Fig. 1.19

High-grade VIN



VIN, vulvar intraepithelial neoplasia. Fig. 1.20

Squamous cell neoplasia, HPV-associated: low-grade and high-grade vulvar intraepithelial neoplasia (VIN) is the precursor of HPV-associated VSCC.

Transformation by HPV involves the same mechanism as in cervical carcinoma, and p16 immunostaining and HPV typing are used similarly in the diagnostic setting.

HPV-associated VSCCs affect younger women compared with HPV-independent VSCCs and have better stage-matched survival than the latter. Histopathological grading has no prognostic value.

Squamous cell neoplasia, HPV-independent: differentiated VIN (dVIN), often associated with lichen sclerosus, is the precursor of HPV-independent VSCC.

Tumours often carry *TP53* mutations, and aberrant p53 immunostaining is seen in dVIN and invasive carcinomas.

The initial site of metastasis from VSCC, both HPV-associated and HPV-independent, is inguinal lymph nodes.

Differentiated VIN (dVIN)

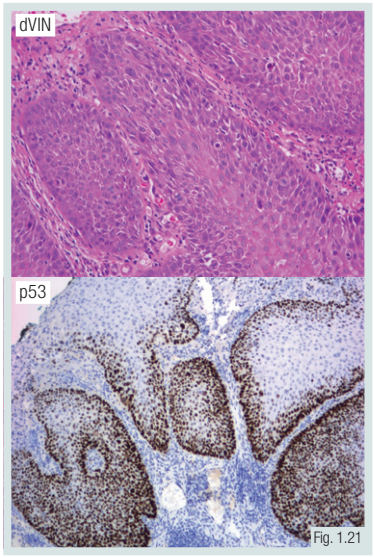


Fig. 1.21

VIN, vulvar intraepithelial neoplasia.

REVISION QUESTIONS

1. Which malignant tumour is most common in the vulva?
2. Does HPV status have a role in classifying VSCC?
3. What is the name of the precursor lesions of VSCC and which immunostains are relevant?

Summary: Histopathology of gynaecological cancers

- Primary ovarian tumours consist of GCTs, SCSTs and epithelial tumours
- The majority of GCTs are benign, and the majority of SCSTs are benign or of low malignant potential
- Tubo-ovarian carcinomas constitute the majority of malignant tumours at this anatomical site, of which HGSC is the most common type
- The majority of malignant uterine tumours are carcinomas, which are grossly divided into endometrioid and non-endometrioid
- TCGA classification has prognostic relevance in uterine cancer, and p53, MMR and *POLE* are surrogate markers for this classification
- The most common uterine sarcomas are LMS and ESS, the latter divided into low-grade and high-grade entities, each with unique fusion genes
- Uterine cervical carcinomas are classified as SCC, adenocarcinoma and neuroendocrine carcinoma
- Cervical adenocarcinomas are divided into HPV-associated and HPV-independent tumours
- The majority of malignant vulvar tumours are VSCCs, which are divided into HPV-associated and HPV-independent tumours
- Genetic predisposition for gynaecological tumours includes *BRCA1/2* mutations in HGSC and MMR gene mutations (Lynch syndrome) in uterine corpus carcinoma, and less often in tubo-ovarian carcinoma

Further Reading

Kurman RJ, Ellenson LH, Ronnett BM (Eds). Blaustein's Pathology of the Female Genital Tract, 7th edition. New York: Springer Nature, 2019.

Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. CA Cancer J Clin 2019; 69:280–304.

Lu KH, Broaddus RR. Endometrial cancer. N Engl J Med 2020; 383:2053–2064.

Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. Hum Pathol 2018; 80:11–27.

Singh N, Gilks CB. Vulval squamous cell carcinoma and its precursors. Histopathology 2020; 76:128–138.

Soslow RA, Tornos C, Park KJ, et al. Endometrial carcinoma diagnosis: use of FIGO grading and genomic subcategories in clinical practice: recommendations of the International Society of Gynecological Pathologists. Int J Gynecol Pathol 2019; 38 Suppl 1 (Iss 1 Suppl 1):S64–S74.

Stolnicu S, Soslow RA. Squamous and glandular epithelial tumors of the cervix: a pragmatical review emphasizing emerging issues in classification, diagnosis, and staging. Surg Pathol Clin 2022; 15:369–388.

WHO Classification of Tumours Editorial Board. Female Genital Tumours. WHO Classification of Tumours, 5th edition, Volume 4. Lyon, France: IARC, 2020.

Image sources: **Fig. 1.1.** Ferlay J, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer, 2020; Available from: https://gco.iarc.fr/today [accessed 24 May 2024]; **1.7.** Lheureux S, et al. Lancet 2019;393:1240-1253; **1.10.** Ryan NA, et al. Obstet Gynaecol 2021;23:9-20; **1.11.** Casey L, Singh N. Int J Gynecol Pathol 2021;40:5-16; **1.14.** Micci F, et al. Cancer 2021;60:160-167; **1.15.** Kaur B. Best Pract Res Clin Obstet Gynaecol 2021;74:3-28; **1.16.** Park KJ. Histopathology 2020;76:112-127. All other figures courtesy of the authors.