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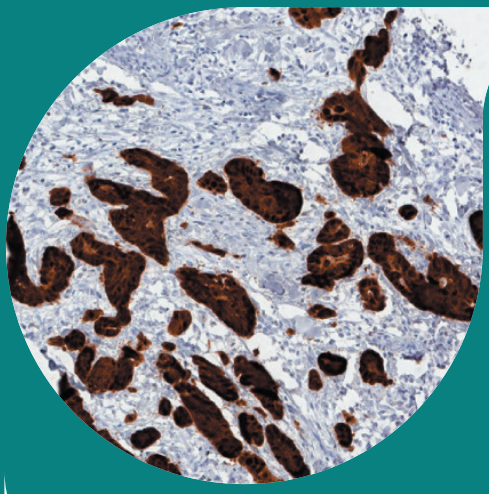
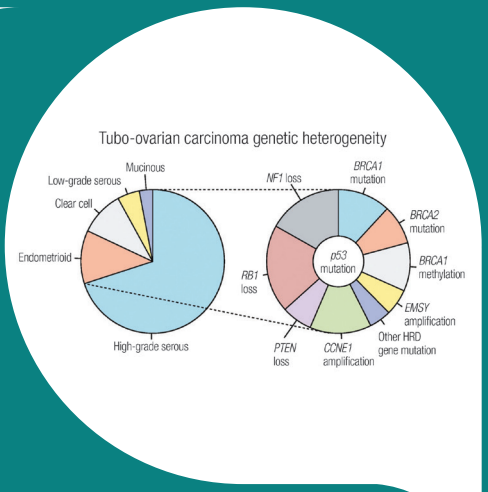
GYNAECOLOGICAL TUMOURS

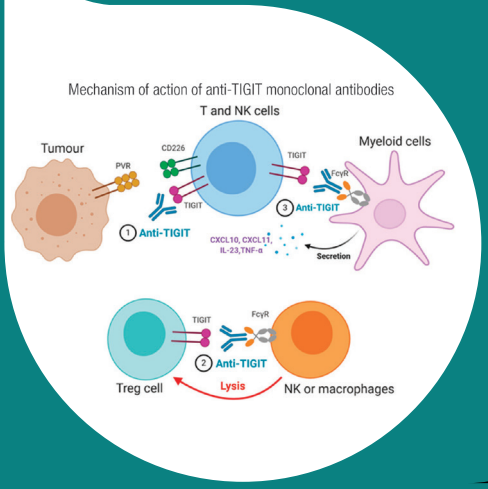
SECOND EDITION

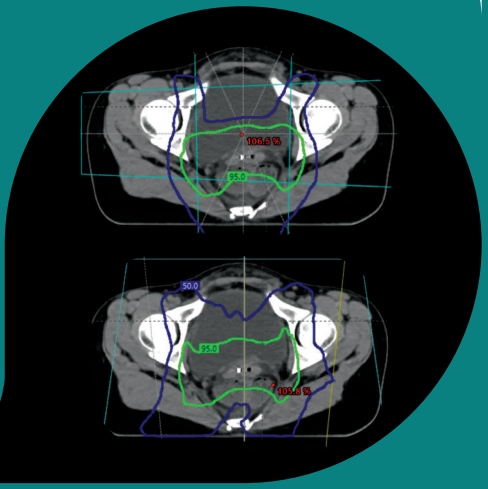
ESSENTIALS *for* CLINICIANS

edited by
Christina Fotopoulou
Antonio González-Martín
Marcia Hall









ESMO Press

GOOD SCIENCE
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Gynaecological Tumours
Essentials for Clinicians

Second edition

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Edited by

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Preface

Almost as soon as the first edition of *Gynaecological Tumours: Essentials for Clinicians* was published in 2017, PARP inhibitors, mentioned with some excitement then, burst on to the scene with aplomb and are now transforming outcomes for a significant proportion of patients with ovarian cancer. Similarly, for those with uterine cancer, the massive increase in understanding of molecular subtypes of this cancer is resulting in a plethora of novel treatment options for some patients, including antiangiogenics and immunotherapy. We are also delighted to report here that novel strategies are beginning to change outcomes for some with relapsed cervical cancer. In addition, the international community is pulling together to pool data and outcomes in rare gynaecological cancers. So, this update to the book is long overdue.

Gynaecological Tumours: Essentials for Clinicians aims to help trainees understand the basics: ranging from pathology and molecular signatures through surgery, radiation and non-surgical therapies for these patients. We are truly grateful to the experts in gynaecological oncology from around Europe for working with the strict formatting requirements that make the series so accessible. We hope that it inspires many to follow personal curiosity and delve deeper into both the science and trial opportunities that should follow for patients with these cancers.

The greatest accolade would be that this edition is out of date as quickly as the last, forcing us to lobby for a third edition.

Marcia Hall MB, BS, PhD
Mount Vernon Cancer Centre, Northwood; Brunel University London, London, UK
On behalf of all editors

Editors

Christina Fotopoulou, MD, PhD

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Christina Fotopoulou is Professor of Gynaecological Cancer Surgery in the Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK and the Deputy Director of the Ovarian Cancer Action Research Centre at Imperial College. She is an Honorary Chair in the Gynaecology Department at the Charité University of Berlin, Germany, where she trained and then later took the role of Vice Director of the Gynaecology Department.

Her surgical and scientific expertise focuses on the management of patients with advanced and relapsed ovarian cancer, profiling of tumour heterogeneity and integration of tumour biology factors with surgical effort under the umbrella of individualisation of surgical care.

Professor Fotopoulou has served as the lead of the Guidelines Committee of the British Gynaecological Cancer Society (BGCS), elected member of the European Society of Gynaecological Oncology (ESGO) council and lead of the ESGO Guidelines Committee and is also a member of the German AGO–Ovarian Cancer Study Group.

She is on the editorial board and reviewer for numerous international gynaecological and oncological journals and is a member of various international oncological committees.

Antonio González-Martín, MD, PhD

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Antonio González-Martín graduated in Medicine from the Universidad de Navarra, Pamplona, Spain and subsequently trained in medical oncology at Hospital Universitario Ramón y Cajal, Madrid, Spain from 1994 to 1997. During 1997, he attended the Mount Sinai School of Medicine in New York, USA as an observer.

Since September 2017 he has been Head of the Medical Oncology Department at Clínica Universidad de Navarra, and in 2020 he was appointed Director of the Cancer Center, Clínica Universidad de Navarra.

Professor González-Martín is an Associate Professor of Medicine at Francisco de Vitoria University, Madrid, Spain and Collaborator Professor at Universidad de Navarra. He obtained his PhD degree at Francisco de Vitoria University in April 2018.

Professor González-Martín is the Chairman of GEICO (Spanish Ovarian Cancer Research Group) and was the President in ENGOT (European Network of Gynaecological Oncological Trials group) for the period 2018–2020. In addition, he is one of the delegates in the Gynecologic Cancer InterGroup (GCIG) and served as Chair of the Ovarian Cancer Committee for the period 2014–2020. He is considered an international expert in gynaecological cancer and has authored several publications and lectured widely on the topic.

Marcia Hall, MB, BS, PhD

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Marcia Hall is Professor of Translational Oncology at Brunel University London, London, UK and a Consultant in Medical Oncology at Mount Vernon Cancer Centre, Northwood, UK. She has a background in managing patients with a wide range of cancer types (gastrointestinal, germ cell, breast) but now focuses solely on the treatment of patients with gynaecological cancers.

Professor Hall's research focus is related to the identification of homologous repair deficiency from circulating (blood samples) factors, and she was the lead for research and development at Mount Vernon Cancer Centre between 2013 and 2021.

Nationally, she has sat on the UK National Cancer Research Institute gynaecological cancers subgroup since 2006 and, internationally, has been a member of the ESMO Educational Publications Working Group (2015–2023; Deputy Chair: 2018–2021).

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Abbreviations

^{18}F-FDG	^{18}F-fluorodeoxyglucose
5-FU	5-fluorouracil
ADC	Antibody–drug conjugate
AFP	Alpha-foetoprotein
AIS	Adenocarcinoma *in situ*
ALT	Alanine aminotransferase
AMH	Anti-Müllerian hormone
AST	Aspartate transaminase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3-related
βHCG	Beta-human chorionic gonadotropin
BEP	Bleomycin, etoposide and platinum
BETi	Bromodomain and extraterminal inhibitor
CA125	Cancer antigen 125
CC	Cervical cancer
CCC	Clear cell carcinoma
CDH6	Cadherin 6
CDK4/6	Cyclin-dependent kinase 4/6
CHK1	Checkpoint kinase 1
ChT	Chemotherapy
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
D&C	Dilatation and curettage
DDR	DNA damage response
DDRi	DDR inhibitor
DFS	Disease-free survival
dMMR	Mismatch repair-deficient
dVIN	Differentiated vulvar intraepithelial neoplasia
EBRT	External beam radiotherapy
EC	Endometrial cancer
ECOG	Eastern Cooperative Oncology Group
EEC	Endometrioid endometrial carcinoma
EGFR	Epidermal growth factor receptor
EMT	Epithelial–mesenchymal transition
ENGOT	European Network of Gynaecological Oncological Trial groups
EOC	Endometrioid ovarian carcinoma
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
ESS	Endometrial stromal sarcoma
ET	Endocrine therapy
EURACAN	European Reference Network for Rare Adult Solid Cancers
EZH2i	Enhancer of zeste homologue 2 inhibitor
FH	Fumarate hydratase
FIGO	International Federation of Gynecology and Obstetrics
FRα	Folate receptor alpha
FSS	Fertility-sparing surgery
GAS6	Growth arrest-specific protein 6
GC	Gemcitabine and carboplatin
GCIG	Gynecologic Cancer InterGroup
GCT	Germ cell tumour
GnRH	Gonadotropin-releasing hormone
GTD	Gestational trophoblastic disease
GTN	Gestational trophoblastic neoplasia
HBOC	Hereditary breast and ovarian cancer
hCG	Human chorionic gonadotropin
HDACi	Histone deacetylase inhibitor
HER2	Human epidermal growth factor receptor 2
HG-ESS	High-grade endometrial stromal sarcoma
HGSC	High-grade serous carcinoma
HIPEC	Hyperthermic intraperitoneal chemotherapy
HNF1β	Hepatocyte nuclear factor 1 beta
HNPCC	Hereditary non-polyposis colorectal cancer
HPV	Human papillomavirus
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRT	Hormone replacement therapy
HSIL	High-grade squamous intraepithelial lesion
HU	Hydroxyurea
ICI	Immune checkpoint inhibitor
IDL	Insertion-deletion loop
IDS	Interval debulking surgery
IHC	Immunohistochemistry
IL2	Interleukin 2
IMRT	Intensity-modulated radiotherapy
i.p.	intraperitoneal
ITC	Isolated tumour cell
LG-ESS	Low-grade endometrial stromal sarcoma
LGSC	Low-grade serous carcinoma
LiLACS	Lymphadenectomy in Locally Advanced Cervical Cancer Study
LMS	Leiomyosarcoma
LN	Lymph node
LND	Lymphadenectomy
LOH	Loss of heterozygosity
LS	Lynch syndrome
LSIL	Low-grade squamous intraepithelial lesion
LVSI	Lymphovascular space invasion
mAb	Monoclonal antibody
MC	Mucinous carcinoma
MIS	Minimally invasive surgery
MMR	Mismatch repair
MOC	Mucinous ovarian cancer
MOGCT	Malignant ovarian germ cell tumour
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability-hypermutated
N-	Node-negative
N+	Node-positive
NACT	Neoadjuvant chemotherapy
NaPi2b	Sodium-dependent phosphate transporter 2b
NCCN	National Comprehensive Cancer Network
NF-κB	Nuclear-factor kappa B
NK	Natural killer
NSMP	No specific molecular profile
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
p53-abn	p53 abnormal
PA	Para-aortic
PALND	Para-aortic lymphadenectomy
PARP	Poly (ADP-ribose) polymerase
PARPi	PARP inhibitor
PCNA	Proliferating cell nuclear antigen
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PE	Pelvic exenteration
PET	Positron emission tomography
PFS	Progression-free survival
PgR	Progesterone receptor
PI3K	Phosphoinositide-3 kinase
PLD	Pegylated liposomal doxorubicin
PLND	Pelvic lymphadenectomy
pMMR	Proficient mismatch repair
POLE	Polymerase epsilon
*POLE*mut	Polymerase epsilon ultramutated
pPS	Partially platinum sensitive
ProMisE	Proactive Molecular Risk Classifier for Endometrial Cancer
PS	Platinum sensitive
PTEN	Phosphatase and tensin homologue
PVR	Poliovirus receptor

QoL	Quality of life
RaNGO	Rare Neoplasms of Gynaecological Origin
Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumours
RFC	Replication factor C
RFS	recurrence-free survival
ROC	Recurrent ovarian cancer
RR	Response rate
RT	Radiotherapy
SCC	Squamous cell carcinoma
SCCOHT	Small cell carcinoma of the ovary, hypercalcaemic type
SCST	Sex cord-stromal tumour
SEER	Surveillance, Epidemiology, and End Results
SEIC	Serous endometrial intraepithelial carcinoma
SF1	Steroidogenic factor-1
SINE	Selective inhibitor of nuclear export
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SLNM	Sentinel lymph node mapping
STIC	Serous tubal intraepithelial carcinoma
STING	Stimulator of interferon genes
TAP	Cisplatin, doxorubicin and paclitaxel
TC	Carboplatin and paclitaxel
TCGA	The Cancer Genome Atlas
TFD	Tumour-free distance
TGFβ	Transforming growth factor beta
TIGIT	T-cell immunoreceptor with Ig (immunoglobulin) and ITIM (immunoreceptor tyrosine-based inhibitory motif)
TMRG	Tumeurs Malignes Rares Gynécologiques
Treg	Regulatory T cell
Trop-2	Trophoblast cell-surface antigen 2
TVUS	Transvaginal ultrasound
UC	Uterine carcinoma
US	Ultrasound
VIN	Vulvar intraepithelial neoplasia
VSCC	Vulvar squamous cell carcinoma
WB	Whole body
WHO	World Health Organization
XPO1	Exportin 1

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Christina Fotopoulou, Antonio González-Martín and Marcia Hall

A

What every oncologist should know

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.

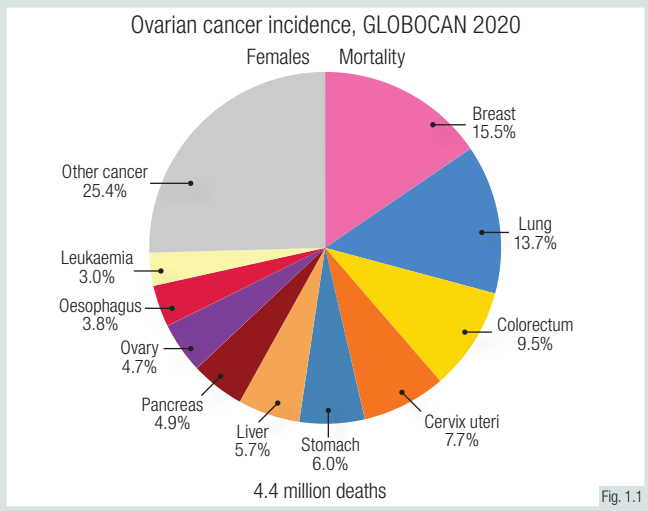


Fig. 1.1

Mature teratoma

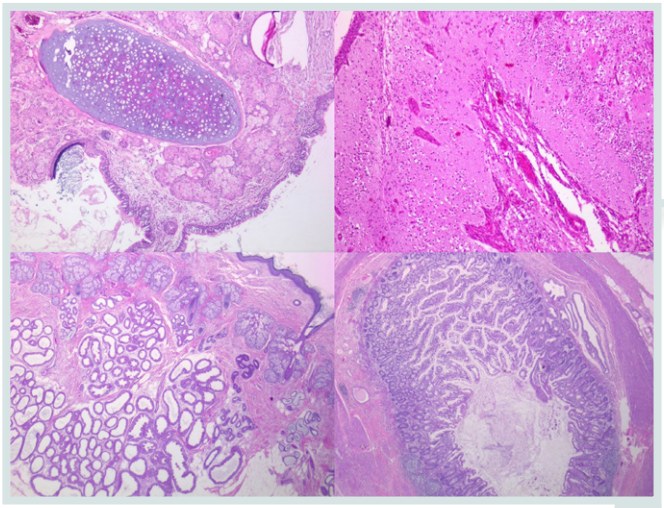


Fig. 1.2

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

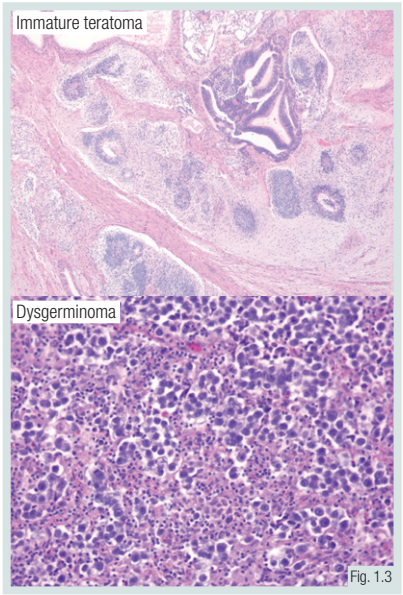


Fig. 1.3

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

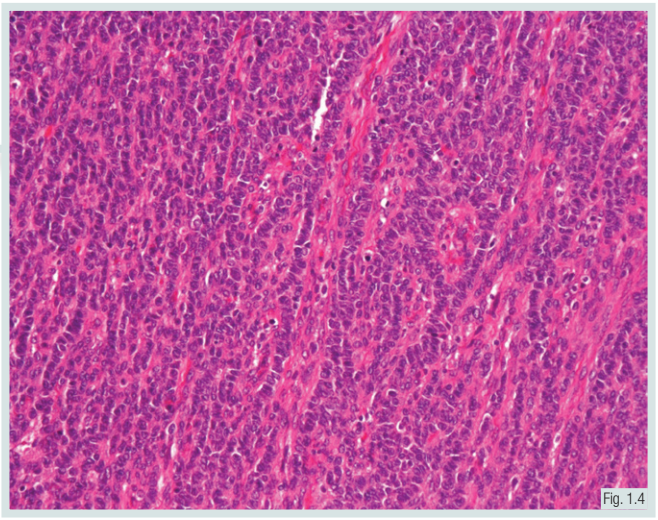
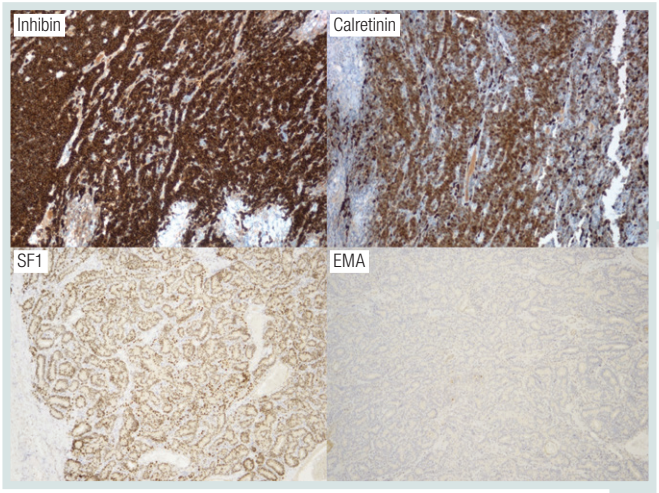


Fig. 1.4

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

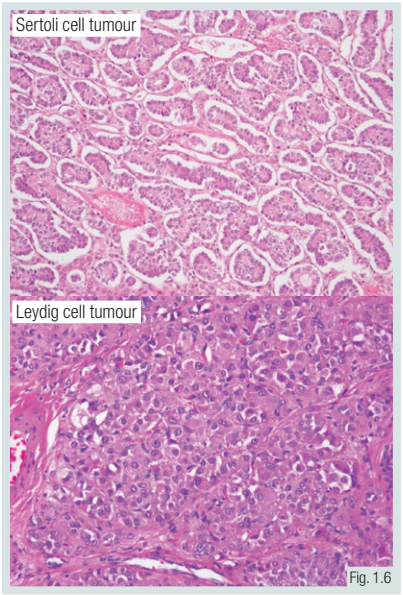


Fig. 1.6

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

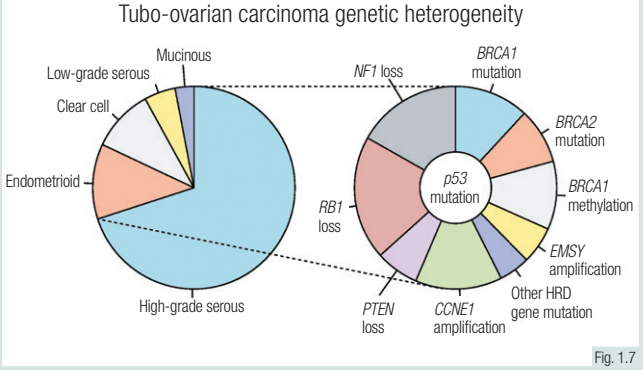
1. Are the majority of SCSTs benign or malignant?
2. What are the useful diagnostic stains for SCSTs?
3. Are there any genetic tests used to classify these tumours?

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).

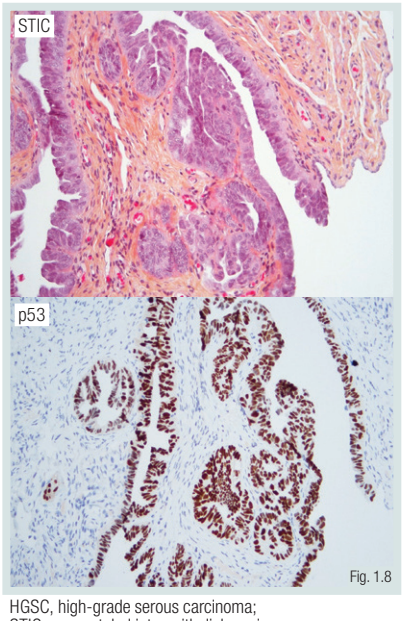
These five histotypes are five different diseases, each with its own pathogenesis, morphology, immunohistochemistry (IHC) profile, genetic features, prognosis and clinical response to chemotherapy (ChT) and targeted therapy.

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.

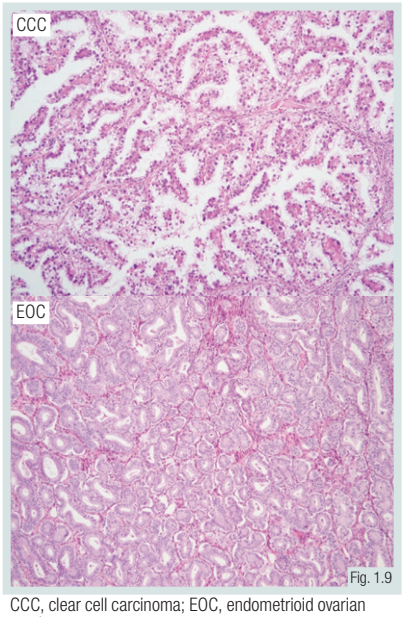
It is a clinically aggressive tumour often diagnosed at an advanced stage. Debulking to no macroscopic disease, ChT and PARP (poly [ADP-ribose] polymerase) inhibition are mainstays of therapy.

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.

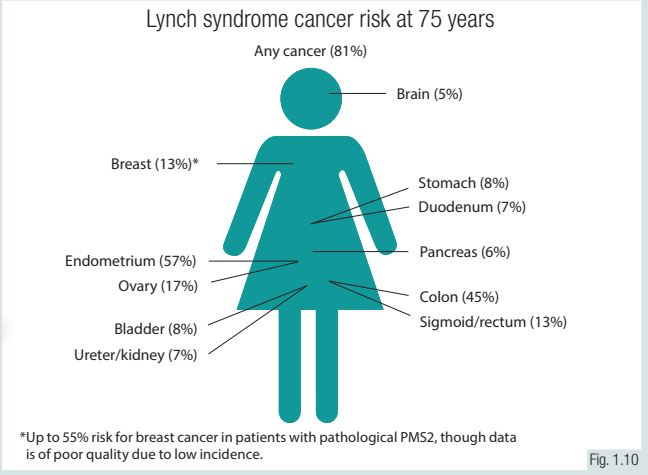


Fig. 1.10

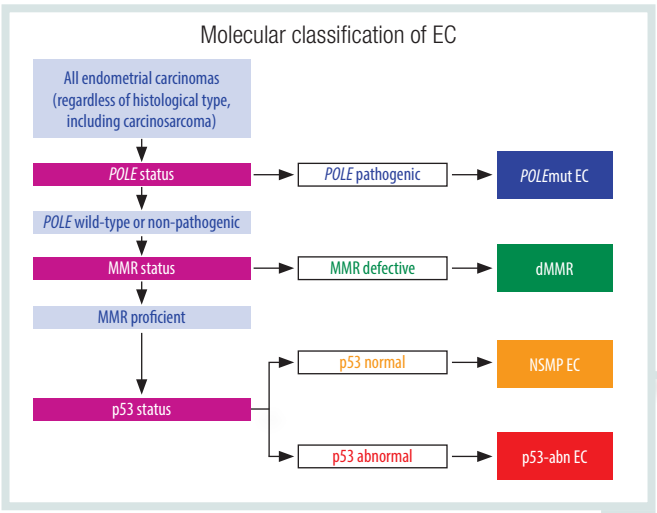


Fig. 1.11

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

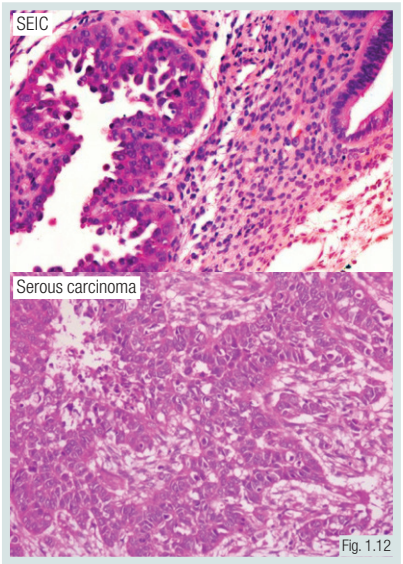


Fig. 1.12

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?

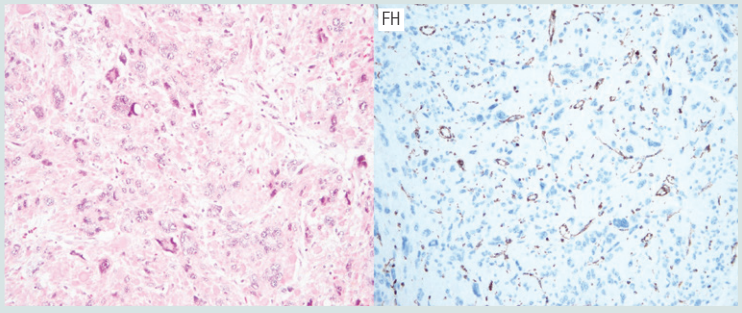
Uterine corpus tumours – Non-epithelial tumours

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

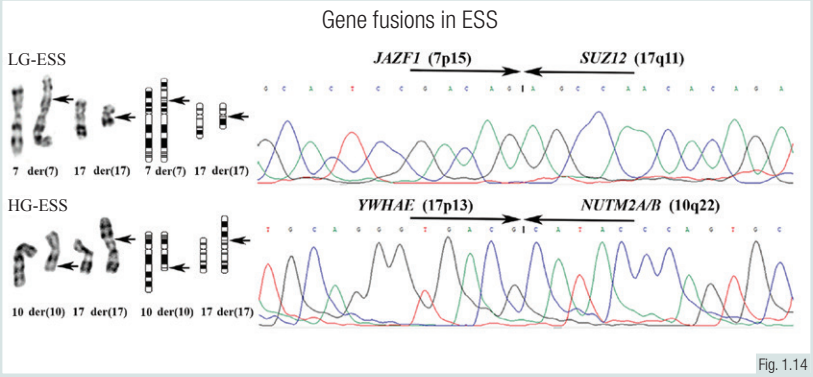


Fig. 1.14

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.

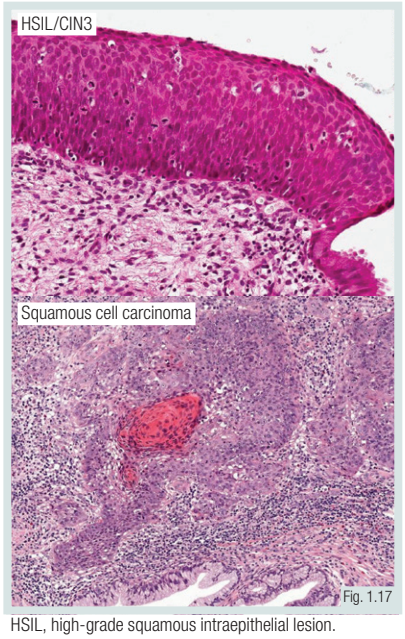
WHO 2014 and IECC 2018 classifications of cervical adenocarcinomas*

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.

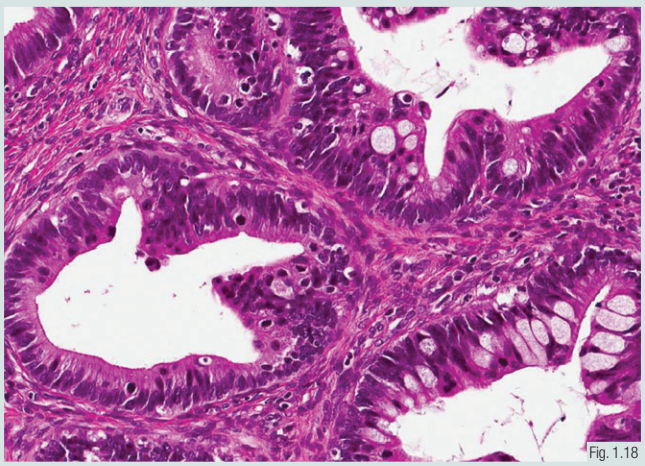
The majority of SCCs are focally- or non-keratinising; grading is not informative of prognosis.

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?

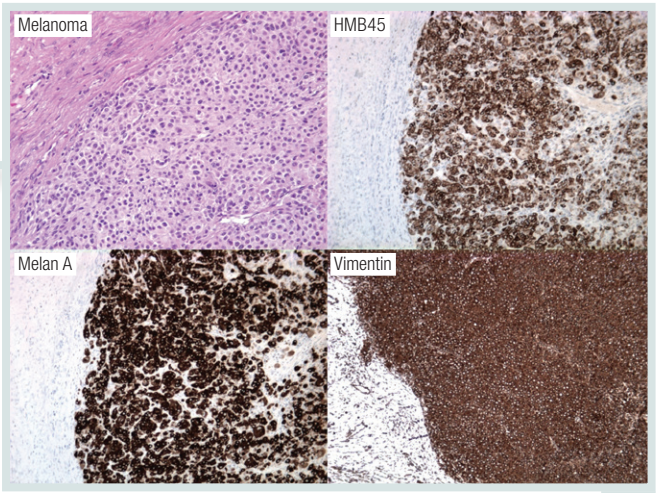
Vulvar tumours

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.

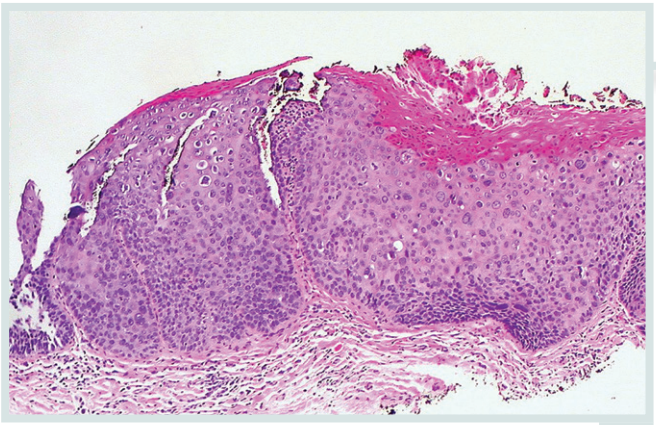
Immunostaining for p16 is a surrogate marker of HPV infection, although there is not full concordance between HPV infection and p16 staining.

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)

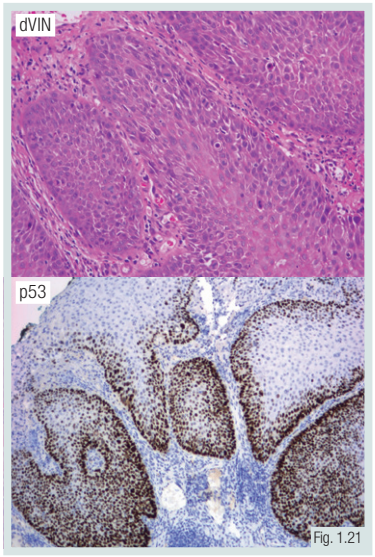


Fig. 1.21

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

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2 Staging and surgical treatment of ovarian cancer

Presumed early stage

Complete surgical staging and tumour removal is a critical prognostic factor for patients with ovarian cancer (OC).

In presumed early-stage OC, only thorough surgical staging can confirm early-stage and potentially reveal occult higher-stage disease. No radiological work-up is equally effective.

In advanced OC, complete resection of all visible disease is the most important step of the initial treatment for potential cure.

Surgical site after retroperitoneal lymph node dissection

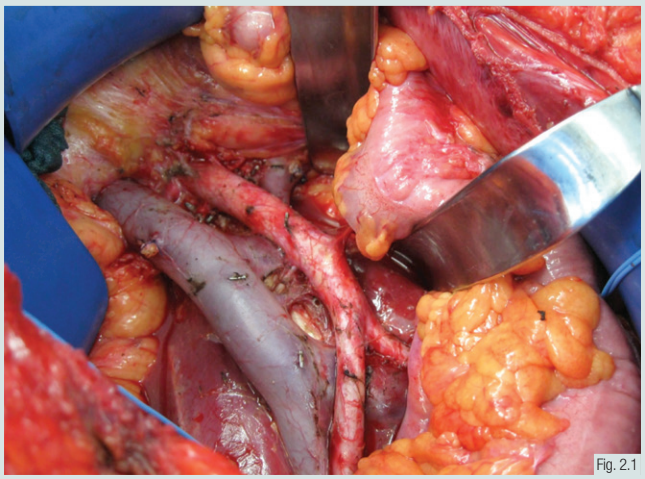


Fig. 2.1

Survival in presumed early-stage OC in correlation with lymph node dissection

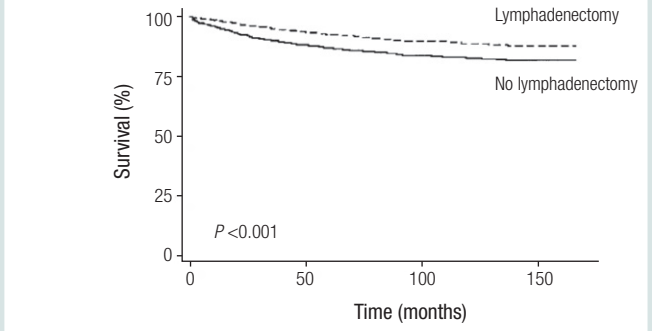


Fig. 2.2

OC, ovarian cancer.

Complete staging in presumed early-stage OC consists of cytology (peritoneal washings), systematic assessment of the abdominal cavity, hysterectomy with bilateral salpingo-oophorectomy; in non-fertility-sparing procedures, omentectomy and peritoneal staging.

A retrospective analysis of patients with stage I OC demonstrated that systematic lymphadenectomy resulted in detection of metastasis in 22% of the patients, compared with 9% with lymph node sampling alone.

Retrospective analyses suggest an improved OS following systematic lymphadenectomy for patients with stage I OC.

It is difficult to assess the individual effect of each staging procedure. However, several analyses have been published showing potential prognostic effects.

Performance of systematic peritoneal biopsies, for example, was shown to be prognostically relevant.

Performance of individual surgical steps may be surrogate parameters for thorough general surgical quality.

Survival in presumed early-stage OC in correlation with surgical staging

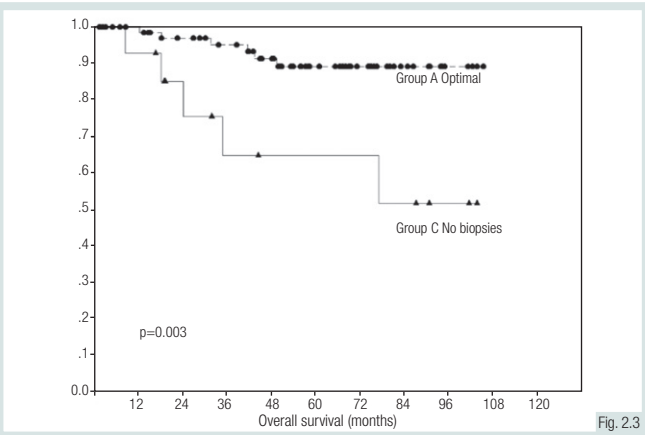


Fig. 2.3

OC, ovarian cancer.

REVISION QUESTIONS

1. Why should surgical staging be performed in presumed early-stage OC?
2. What are the steps of surgical staging in presumed early-stage OC?
3. Is systematic lymphadenectomy important?

Fertility-sparing surgery and surgical approach

If OC is confined to one ovary, fertility-sparing surgery (FSS) should be discussed with women of childbearing potential.

FSS can safely be offered to patients with low-grade stage I OC. However, the recurrence rate is higher in those with high-grade serous OC.

Patients will need careful counselling, and two staging procedures may be optimal for some.

Literature review of results of conservative management in epithelial OC (7 series reported including >10 cases)

	Stage IA, grade 1	Stage IA, grade 2	Stage IA, grade 3	Stage IC, grade 1	Stage IC, grade 2	Stage IC, grade 3
Italian series Zanetta et al Colombo et al	1 recurrence among 24 patients	3 recurrences among 8 patients	1 recurrence among 4 patients	No recurrence among 10 patients	1 recurrence among 6 patients	No recurrence among 3 patients
American series Schilder et al	2 recurrences among 33 patients	2 recurrences among 6 patients	No recurrence among 3 patients	No recurrence among 5 patients	1 recurrence among 3 patients	No recurrence among 2 patients
French series Morice et al	1 recurrence among 13 patients	4 recurrences among 14 patients	1 recurrence among 3 patients	2 recurrences in 2 patients	No patient	1 recurrence in 1 patient
Bogfeldt et al	No recurrence among 8 patients	No recurrence in 1 patient	No patient	No patient	No patient	1 recurrence in 1 patient
Park et al	1 recurrence among 29 patients	No recurrence in 3 patients	4 recurrences in 4 patients	1 recurrence in 15 patients	1 recurrence in 2 patients	2 recurrences in 4 patients
Anchezar et al	1 recurrence among 10 patients	No patient	1 recurrence in 1 patient*	No recurrence in 3 patients	No recurrence in 1 patient	No recurrence in 1 patient
Satoh et al	5 recurrences among 95 patients	No recurrence in 13 patients	2 recurrences in 3 patients	5 recurrences among 65 patients	No recurrence in 2 patients	1 recurrence in 3 patients
Total	11 (5%) recurrences among 207 patients	9 (20%) recurrences among 45 patients	8 (45%) recurrences among 18 patients	8 (8%) recurrences among 100 patients	4 (29%) recurrences among 14 patients	5 (3%) recurrences among 15 patients

*Patient considered as having a stage IA, grade 3 tumour after pathological review of the initial tumour at the time of the recurrence.

OC, ovarian cancer.

Fig. 2.4

Laparoscopic view of the right upper abdomen

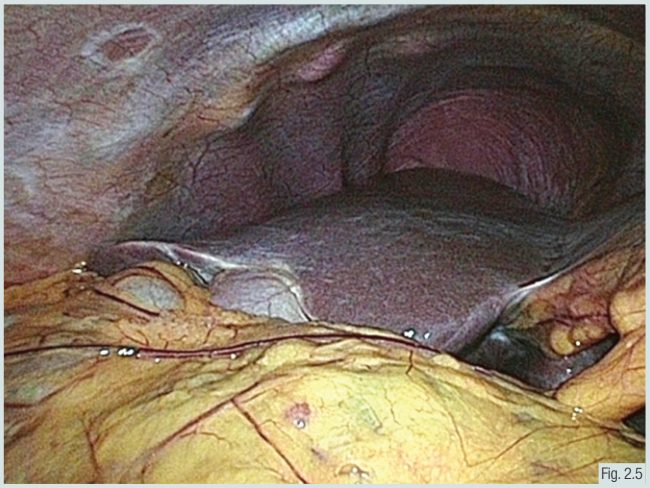


Fig. 2.5

Laparotomy is the standard approach for staging surgery in presumed early- as well as advanced-stage OC.

Laparoscopic as well as robotic surgical approaches have been assessed in several small series, with a view to replacing open staging surgery, especially in patients with presumed early-stage OC.

Methodological limitations prohibit definitive conclusions regarding the utility of minimally invasive surgery in this setting.

Given the biology and tumour spread of high-grade OC, complete tactile and visual exploration of the abdomen is best performed through open surgery.

To avoid understaging, e.g. missing peritoneal and retroperitoneal spread, laparoscopic or robotic surgical staging of presumed early-stage OC are not recommended outside of clinical trials.

Open surgical view of the right upper abdomen with peritoneal carcinomatosis only visible after mobilisation of the liver

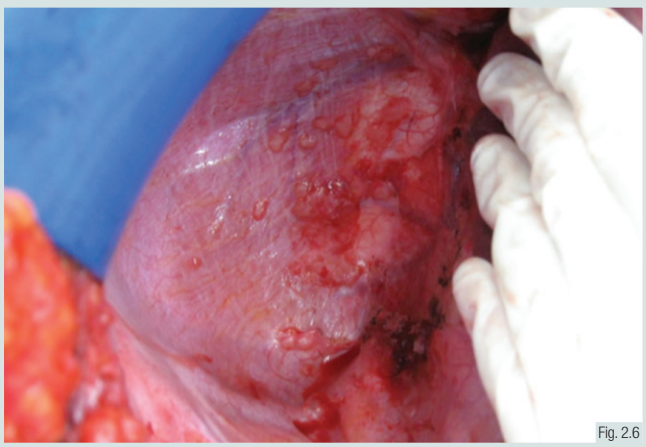


Fig. 2.6

REVISION QUESTIONS

1. In which instance might FSS be considered and discussed with the patient?
2. What are the risks of FSS?
3. What are the potential problems of laparoscopic or robotic staging surgery in presumed early-stage OC?

Advanced stages

For optimal surgical assessment and resection in patients with advanced OC, laparotomy with an adequate retractor system is a key prerequisite.

Specialist gynaecological–oncological surgical teams, including surgeons, anaesthetists, nurses and operating-department staff, are vital.

Surgery for patients with OC should only be performed in specialist centres where such teams and support are available.

Example of adequate retraction for optimal surgical access in OC surgery

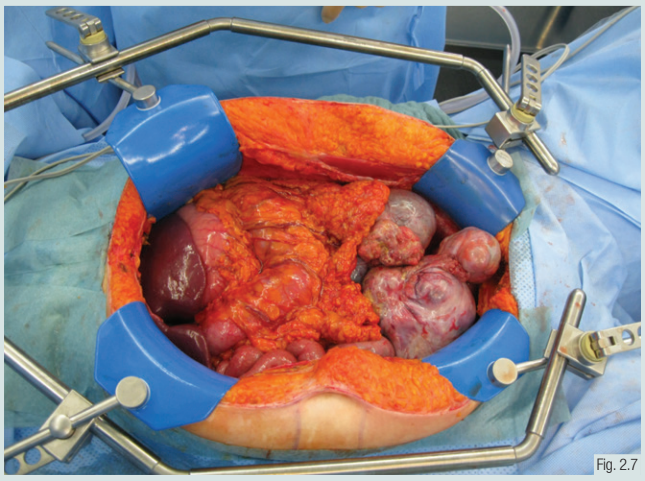


Fig. 2.7

OC, ovarian cancer.

Inspection of the bursa omentalis

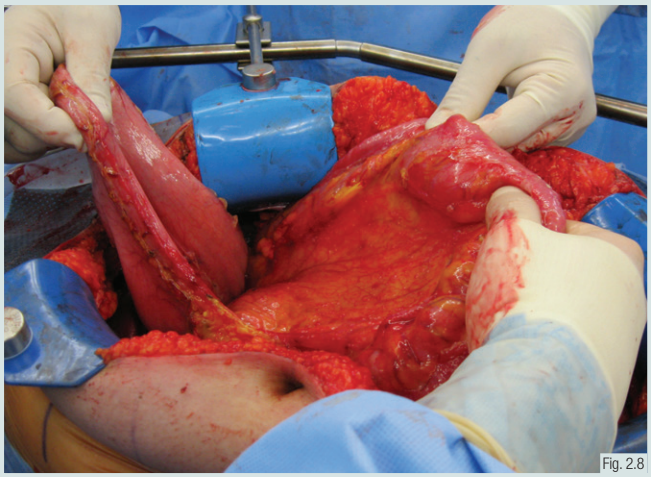


Fig. 2.8

Numerous studies have evaluated the use of diagnostic laparoscopy to estimate operability.

The identification of extensive disease via laparoscopy (e.g. involvement of mesentery or small bowel serosa) reduces the time of recovery (as opposed to standard laparotomy), allowing prompt initiation of neoadjuvant chemotherapy (NACT).

For some patients, diagnostic laparoscopy may confirm that they are not candidates for complete cytoreduction.

Diagnostic laparoscopy can be useful in patients with equivocal findings on initial gynaecological or radiological work-up, as well as a history of other malignancies; however, it may not always predict operability.

This picture shows findings of a premenopausal woman, with a history of gastric cancer 10 years prior as well as a strong family history of breast cancer and OC. Histology after diagnostic laparoscopy revealed metastases of the gastric cancer.

Peritoneal carcinomatosis

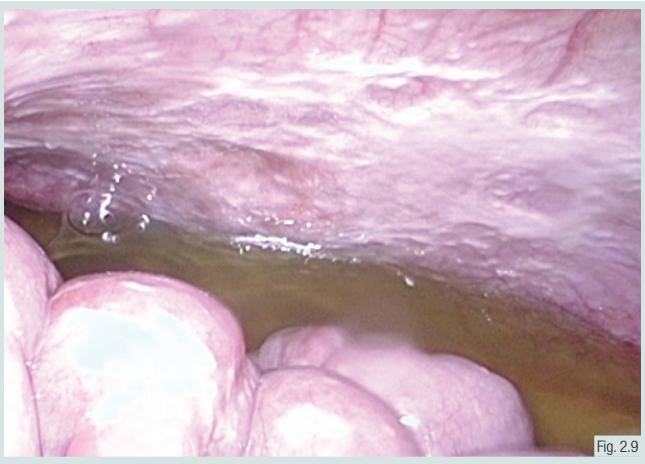


Fig. 2.9

REVISION QUESTIONS

1. Why should patients with OC receive surgery in specialised centres?
2. What are the potential limitations of diagnostic laparoscopy in advanced OC?
3. How can laparoscopy be useful in the work-up of patients with suspected OC?

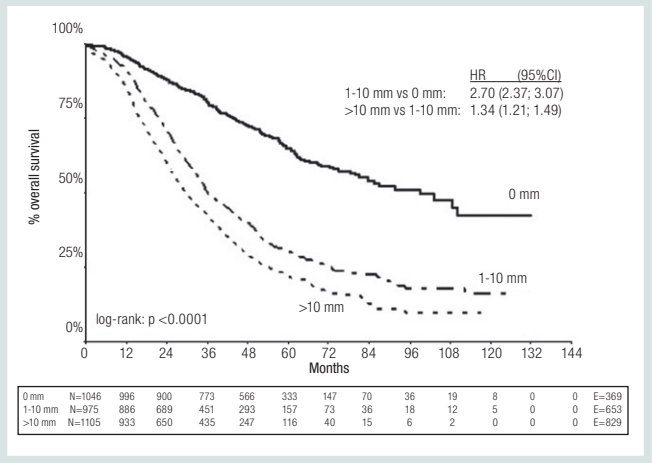
Surgical principles in advanced disease

The central aim of all surgical effort in patients with advanced OC should be complete gross resection of all visible tumour.

Patients without residual disease after surgery have a 5-year survival rate of >60%, whereas this drops to ~25% in those with residual tumour.

It is important to note that patients with small residual disease (1–10 mm) have a statistically significant longer survival than those with larger residuals (>1 cm).

PFS outcome in relation to size of residual tumour



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. Fig. 2.10

Pelvic peritoneum (area in green) and access for the extraperitoneal approach

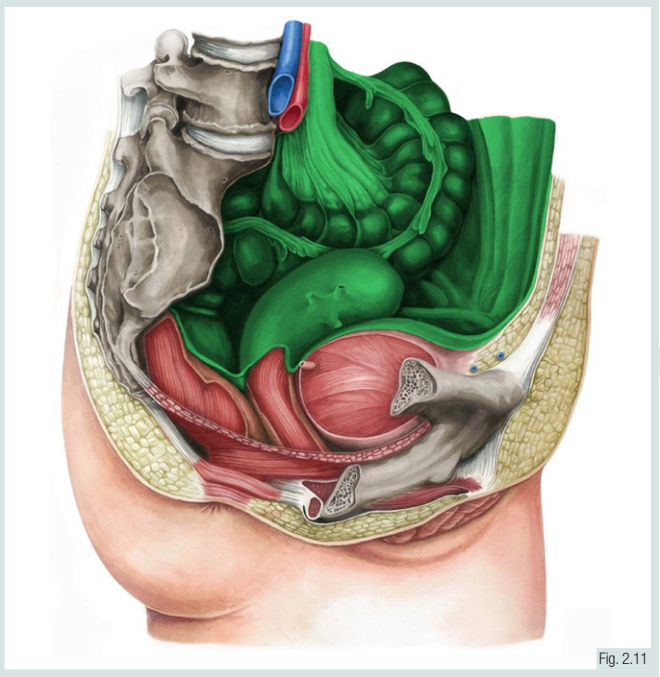


Fig. 2.11

Advanced OC usually spreads over the peritoneum of the pelvis, as well as throughout the abdomen.

A major principle of surgery in advanced OC is the extraperitoneal *en-bloc* resection of the peritoneum together with the tumour.

Resected *en-bloc* specimen of uterus, pelvic peritoneum and sigmoid colon

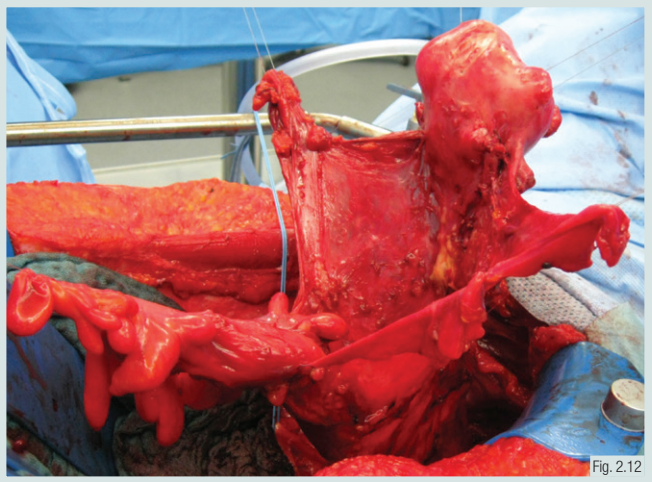


Fig. 2.12

At primary surgery for advanced OC, the pelvis can almost always be cleared of tumour with this approach.

Rectosigmoid resection is necessary in ~50%–60% of patients. Usually, primary anastomosis can be safely performed; the incidence of stomas is generally less than 10%.

REVISION QUESTIONS

1. What is the primary aim of cytoreductive surgery in advanced OC?
2. How often can complete cytoreduction be achieved with upfront debulking surgery?
3. What is the major principle of pelvic surgery in advanced OC?

Surgical principles in advanced disease (continued)

Tumour cells and subsequent peritoneal carcinomatosis can spread throughout the abdomen within the circulating ascitic fluid.

Arrows and green shading indicate common areas for peritoneal implants of OC which will need removing if affected.

This further illustrates the importance of open surgery for advanced OC.

Direction of flow of ascitic fluid results in specific peritoneal disease sites

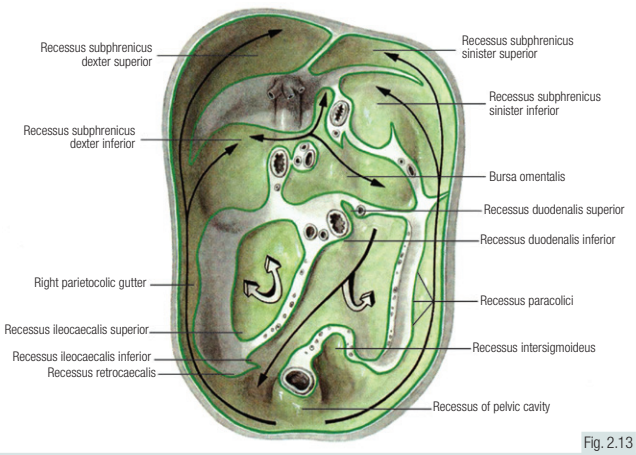


Fig. 2.13

Peritoneal stripping of the left diaphragm after thorough liver mobilisation

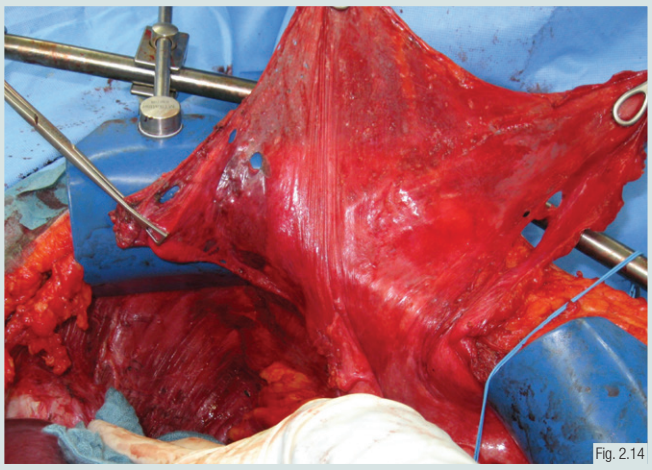


Fig. 2.14

Large areas of peritoneum from different parts of the abdomino–pelvic cavity are usually resected during debulking surgery.

Splenectomy is necessary in ~20% of patients at primary surgery. It is commonly performed *en bloc* with the omentum.

NACT with interval debulking surgery (IDS) is thought to reduce surgical morbidity, compared with upfront debulking followed by adjuvant chemotherapy. Although widely practised, this remains controversial.

NACT and IDS have been compared with upfront debulking in four prospective randomised trials, all of which showed no difference in survival; however, issues of surgical quality have been raised (e.g. resection to zero residual disease in <20% patients).

The results of the TRUST trial (NCT02828618) conducted in high quality-certified surgical centres are awaited.

Proportion of patients in randomised primary versus interval surgery clinical trials where zero residual disease was achieved

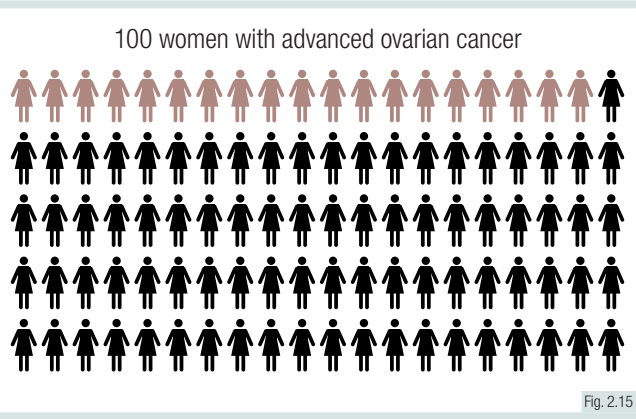


Fig. 2.15

REVISION QUESTIONS

1. Which are the abdominal regions that must be explored during surgery, due to their likelihood of being affected by OC?
2. How often is a splenectomy necessary in tumour debulking for advanced OC?
3. What are the potential advantages/disadvantages of NACT in advanced OC?

Summary: Staging and surgical treatment of ovarian cancer

- Adequate surgical staging and complete tumour removal without spillage are the key aims in surgery for presumed early-stage OC
- FSS can be offered under specific circumstances to patients with childbearing potential
- Minimally invasive surgery for the surgical staging of presumed early-stage OC has not yet been established routinely in current guidelines
- Complete gross resection is the main objective of surgery in advanced OC
- In experienced centres, complete resection can be achieved in the majority of patients
- Multivisceral surgery is often necessary to achieve complete gross resection
- If complete resection is achieved, patients with advanced OC have a 5-year survival of >60%
- NACT and IDS can be an alternative to primary debulking surgery for selected patients with either tumour spread or severe medical conditions that preclude extensive surgery
- To assess the role of NACT, trials with adequate surgical radicality are needed

Further Reading

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Image sources: **Fig. 2.2.** Chan JK, et al. Obstet Gynecol 2007;109:12-19; **2.3.** Timmers PJ, et al. Int J Gynecol Cancer 2010;20:1142-1147; **2.4.** Morice P, et al. Int J Gynecol Cancer 2011;21:951-963; **2.10.** du Bois A, et al. Cancer 2009;115:1234-1244; **2.11.** https://www.kenhub.com/en/library/anatomy/recesses-of-the-peritoneal-cavity; **2.13.** Rickenbacher J, et al. Lanz/Wachsmuth Praktische Anatomie. Berlin Heidelberg: Springer-Verlag, 2003. All other figures courtesy of the authors.

3 Systemic treatment of ovarian cancer

Early- and late-stage disease

In patients with optimally surgically-staged early ovarian cancer (OC), adjuvant platinum chemotherapy (ChT) improves overall survival (OS) for high-risk FIGO (International Federation of Gynecology and Obstetrics) stage I disease (grade 2/3, stage IB/C).

There is also an OS benefit for suboptimally staged early OCs (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.46–0.85).

There is no good evidence to suggest that addition of paclitaxel to single-agent carboplatin has any benefit in this setting.

Effect of adjuvant platinum ChT (10-year OS) for patients with FIGO stage I OC

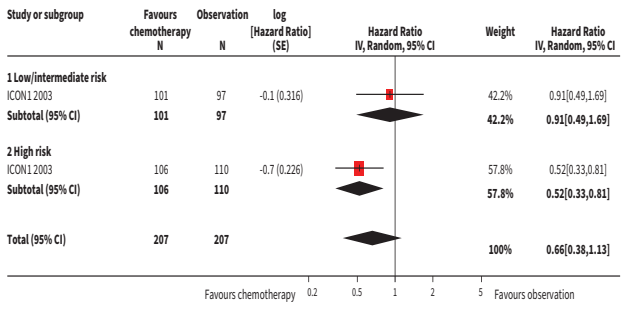


Fig. 3.1

ChT, chemotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IV, interval variable; OC, ovarian cancer; OS, overall survival; Random, random effect model; SE, standard error.

Phase III randomised studies comparing NACT to PS plus adjuvant ChT

Study group	EORTC (Vergote) EORTC 55971	MRC-CTU (Kehoe) CHORUS	JCOG (Yoshikawa) JCOG0602
Stage	Stage IIIC/IV	Stage III/IV	Stage III/IV
Necessity for biopsy/ cytology	FNA cytology allowed, biopsy if possible	Neither biopsy nor cytology necessary	Cytology necessary, biopsy allowed
Tumour marker	CA125/CEA ratio >25	CA125/CEA ratio >25	CA125 >200 U/mL; CEA <20 ng/mL
Regimen	Platinum and taxane	Platinum-based	Platinum and taxane
Chemotherapy cycles (n)	NACT 3 total 6	NACT 3 total 6	NACT 4 total 8
Planned number of patients	704	150 (phase II) + 400 (III)	300
Start date	September 1998	March 2004 (phase III part)	November 2006
Accrual period	4 years	4 years	3 years
Study status	Closed 2006	Closed 2011	Closed 2011
Study design	Non-inferiority	Non-inferiority	Non-inferiority
Outcomes			
Residual disease PS vs NACT	<1 cm residual disease: 48% vs 83%	No residual disease: 15% vs 35%	<1 cm residual disease: 37% vs 82%
Overall survival PS vs NACT	29m vs 30m	22.6m vs 24.1m	49m vs 44.3m

Fig. 3.2

CA125, cancer antigen 125; CEA, carcinoembryonic antigen; ChT, chemotherapy; EORCT, European Organisation for Research and Treatment of Cancer; FNA, fine needle aspiration; JCOG, Japan Clinical Oncology Group; m, month; MRC-CTU, Medical Research Council Clinical Trials Unit; NACT, neoadjuvant chemotherapy; PS, primary surgery.

Although surgery is recommended by international guidelines for OC, for complex reasons, many patients are still not offered surgery (e.g. 44% in the UK, 34% in the USA, as per the SEER [Surveillance, Epidemiology, and End Results] database).

Surgery, whether primary or interval, results in superior survival outcomes compared to ChT alone.

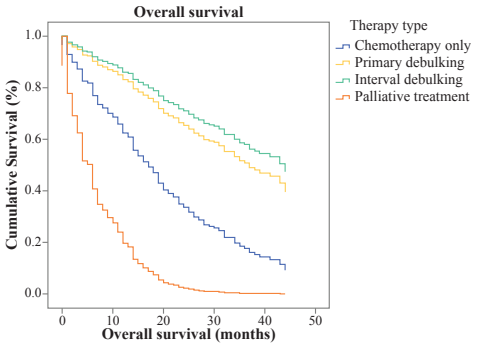
The TRUST and SUNNY studies are yet to report. TRUST involved only surgical centres whose primary surgery complete resection rates were at least 50% and addresses the timing of surgery (upfront versus interval) when optimal primary cytoreduction seems feasible.

Carboplatin plus paclitaxel (TC) is non-inferior to cisplatin plus paclitaxel and is recommended for women with FIGO stage II–IV OC.

Conventionally, surgery was undertaken prior to adjuvant ChT; but many patients are too sick at diagnosis for major surgery and are offered neoadjuvant ChT (NACT) with interval surgery.

Three trials have demonstrated that NACT and interval debulking is non-inferior when complete primary debulking is not possible.

Omitting maximal effort surgery significantly impacts OS



Variable	HR	95% CI	p
Histology (non-serous vs serous)	1.6	1.04–2.61	**0.031**
ECOG status (3/4 vs 1/2)	1.9	1.15–3.13	**0.012**
Primary surgery vs chemotherapy alone*	0.39	0.22–0.67	**0.001**
IDS vs chemotherapy alone*	0.315	0.188–0.52	**<0.001**
Palliative alone vs chemotherapy alone	3.43	1.51–7.81	**0.003**
n.s.: centre (A vs B), age (per year increase), FIGO (III vs IV), grade (low vs high), ethnicity			

*Protective.

Fig. 3.3

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; n.s., no significant effect on patient's survival; OS, overall survival.

REVISION QUESTIONS

1. How should patients with early FIGO stage I OC be managed after surgery?
2. How important is surgery in patients with stage II–IIIC OC?
2. What is the current 'gold standard' ChT for stage II–IV patients?

Adjuvant and maintenance options

In a Japanese population, weekly paclitaxel with 3-weekly carboplatin improved progression-free survival (PFS)/OS (JGOG 3016), though weekly dose-dense ChT showed no PFS/OS benefit over 3-weekly ChT in a predominantly European population (ICON8).

Quality of life (QoL) scores were equivalent at 9 months for patients in the ICON8 trial; extra fatigue and poorer QoL have been observed during treatment for those on weekly regimens.

Paclitaxel-induced neuropathy is related to dose: in the 3-weekly group symptom onset was earlier, in the weekly groups neuropathy developed gradually but lasted longer.

ICON8: overall survival of dose-dense vs 3-weekly ChT

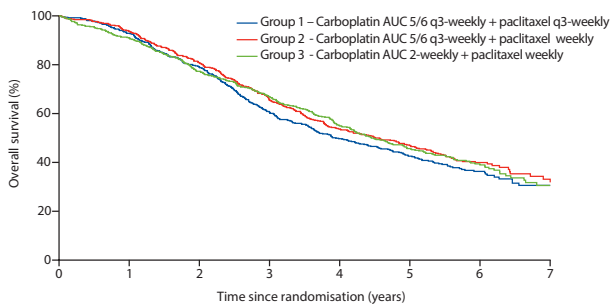


Fig. 3.4

AUC, area under the curve; ChT, chemotherapy.

ICON8: RECIST and GCIG CA125 response to NACT

	Group 1	Group 2	Group 3	Total
RESIST response				
Complete response	8/182 (4%)	6/195 (3%)	7/187 (4%)	21 (4%)
Partial response	102/182 (56%)	119/195 (61%)	106/187 (57%)	327 (58%)
Stable disease	61/182 (34%)	60/195 (31%)	62/187 (33%)	183 (32%)
Progressive disease	11/182 (6%)	10/195 (5%)	12/187 (6%)	33 (6%)
Non-measurable disease at baseline	29	27	29	85
Total (including non-measurable)	211	222	216	649
GCIG CA125 response*				
Yes	198/240 (83%)	204/243 (84%)	208/244 (85%)	610 (84%)
No	42/240 (18%)	39/243 (16%)	36/244 (15%)	117 (16%)
Total	240	243	244	727

*Assessable patients had a baseline CA125 of at least twice the upper limit of normal.

Fig. 3.5

CA125, cancer antigen 125; GCIG, Gynecologic Cancer InterGroup; NACT, neoadjuvant chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumours.

Of the 548 patients with Response Evaluation Criteria in Solid Tumours (RECIST)-evaluable disease in the ICON8 trial, 62% had complete or partial response and 84% a cancer antigen 125 (CA125) response according to Gynecologic Cancer InterGroup (GCIG) criteria. Only 6% progressed.

PFS outcomes were similar for those with RECIST response and those with stable disease (RECIST criteria).

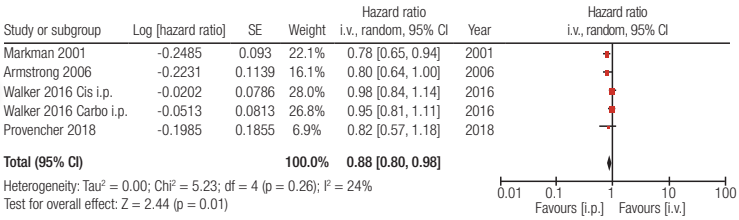
Complete surgical resection was achieved in 42% of patients with stable disease (RECIST criteria) after 3–4 cycles of NACT. Such patients should not be denied interval surgery.

The National Comprehensive Cancer Network (NCCN) guidelines continue to recommend intraperitoneal (i.p.) ChT for selected OC patients with <1 cm residual disease. However, based on the results of GOG-252, the European Society for Medical Oncology (ESMO) guidelines do not.

Tunnelled catheters and ports have improved the ability to deliver ChT intraperitoneally. These can be placed surgically or radiologically over the costal margin or superior anterior iliac crest.

HIPEC (hyperthermic i.p. ChT), a single administration of heated ChT at surgery, is under evaluation; potentially less toxic with similar benefit but there may be incremental OS advantage for each cycle of i.p. platinum/taxane received.

Meta-analyses have shown that i.p. ChT may offer a PFS and OS benefit



Carbo, carboplatin; ChT, chemotherapy; CI, confidence interval; Cis, cisplatin; i.p., intraperitoneal; i.v., intravenous; OS, overall survival; PFS, progression-free survival; SE, standard error.

Fig. 3.6

REVISION QUESTIONS

1. How do adverse effects differ in relation to weekly versus 3-weekly scheduling of paclitaxel?
2. What are the important elements to consider before proposing interval surgery to patients receiving NACT?
3. What is the value of i.p. ChT compared with intravenous adjuvant ChT in stage II–IIIC OC?

Maintenance treatment and follow-up

The ICON7 and GOG-0218 trials demonstrated a benefit for the addition of maintenance bevacizumab following ChT plus bevacizumab in patients with high-risk OC (>1 cm residual disease, not suitable for primary surgery, or stage IV disease).

The outcome of the JGOG 3016 trial prompted theories that the antiangiogenic properties of weekly paclitaxel may result in similar PFS/OS benefits to bevacizumab.

ICON8B explored if paclitaxel weekly rather than 3-weekly, with carboplatin and bevacizumab, improves outcomes in high-risk stage III/IV OC.

Scheduling paclitaxel improves mPFS by 5.5 months

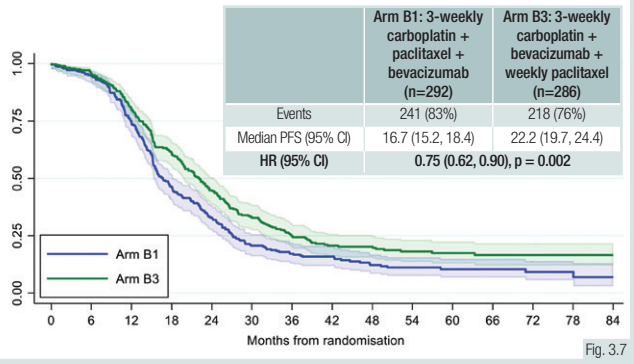


Fig. 3.7

CI, confidence interval; HR, hazard ratio; mPFS, median PFS; PFS, progression-free survival.

PARPis following response to front-line platinum ChT improve PFS

Trial name	SOLO 1	PAOLA1	PRIMA	ATHENA-MONO	PRIME
PARPi	Olaparib 24m (n=260) vs placebo (n=131)	Bevacizumab + olaparib 24m (n=535) vs bevacizumab + placebo (n=267)	Niraparib 36m (n=487) vs placebo (n=246)	Rucaparib 24m (n=427) vs placebo (n=111)	Niraparib 36m (n=255) vs placebo (n=129)
Other eligibility	FIGO III/IV All *BRCA*m	FIGO III/IV Bevacizumab with first-line ChT	All had residual disease	–	Two groups: CR and PR after ChT/primary surgery
Outcomes					
mPFS (ITT)	56m vs 13.8m (HR = 0.33)	22.1m vs 16.6m (HR = 0.59)	13.8m vs 8.2m (HR = 0.62)	20.2m vs 9.2m (HR = 0.52)	24.8m vs 8.3m (CR, HR = 0.44) 16.5m vs 8.3m (PR, HR = 0.27)
HRD+ popn (inc.*BRCA*m)	–	37.2m vs 17.7m (HR = 0.32)	21.9m vs 10.4m (HR = 0.43)	28.7m vs 11.3m (HR = 0.47)	NR vs 11m (HR = 0.48)
HRD- popn	–	16.9m vs 16.0m (HR = 0.92)	8.1m vs 5.4m (HR = 0.68)	12.1m vs 9.1m (HR = 0.65)	16.5 vs 5.5m (HR = 0.41)
mOS	NR vs 65m (NS)	N/A	N/A	N/A	N/A

Fig. 3.8

BRCAm, BRCA-mutant; ChT, chemotherapy; CR, complete response; HR, hazard ratio; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intention-to-treat; m, month; mOS, median overall survival; mPFS, median progression-free survival; N/A, not applicable; NR, not reached; NS, not significant; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; popn, population; PR, partial response.

Following completion of adjuvant ChT, patients may be eligible for other maintenance therapies including poly (ADP-ribose) polymerase inhibitors (PARPis).

All patients should have germline and somatic *BRCA* testing as well as homologous recombination deficiency (HRD) testing, as patients with *BRCA* mutations/HRD benefit most from maintenance PARPi ± bevacizumab.

HRD testing is not perfect. Scoring represents the presence/absence of genomic scars such as loss of heterozygosity (LOH), telomeric allelic imbalance and large-scale transitions as a surrogate for HRD.

Reasons for follow-up:

- Detect curative disease
- Identify relapse without unnecessary investigations
- Reassure and deal with ongoing toxicity
- Collect research data
- Educate and help patients plan for the future

70% of patients with stage III/IV OC will relapse despite optimal surgery and ChT. Response to second-line ChT may be predicted by the progression-free interval following first-line treatment.

Original GCIG classification of platinum responsiveness

Classification	Definition
Platinum-sensitive (PS)	Progress with an interval of >12 months after completion of ChT
Partially PS (pPS)	Progress with an interval of between 6–12 months after completion of ChT
Platinum-resistant (PR)	Progress with an interval of <6 months after completion of ChT
Platinum-refractory (PRef)	Progress during or within 4 weeks after completion of ChT

Fig. 3.9

ChT, chemotherapy; GCIG, Gynecologic Cancer InterGroup.

This is somewhat theoretical; the platinum-free interval should be considered a spectrum

REVISION QUESTIONS

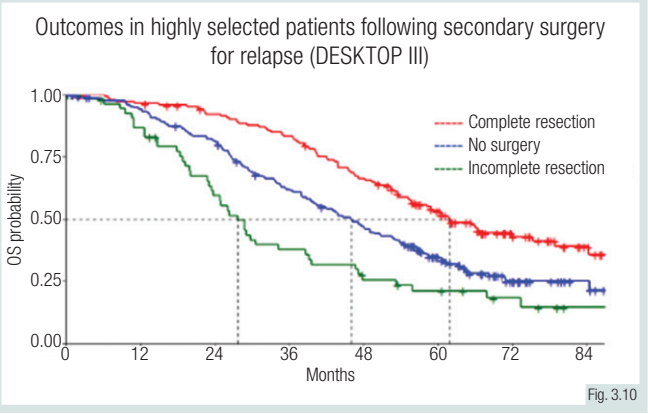
1. Which patients benefit from weekly paclitaxel with bevacizumab/carboplatin?
2. Who should be considered for maintenance PARPi therapy?
3. What is the role of follow-up after primary treatment for patients with OC?

Management of patients with relapsed OC

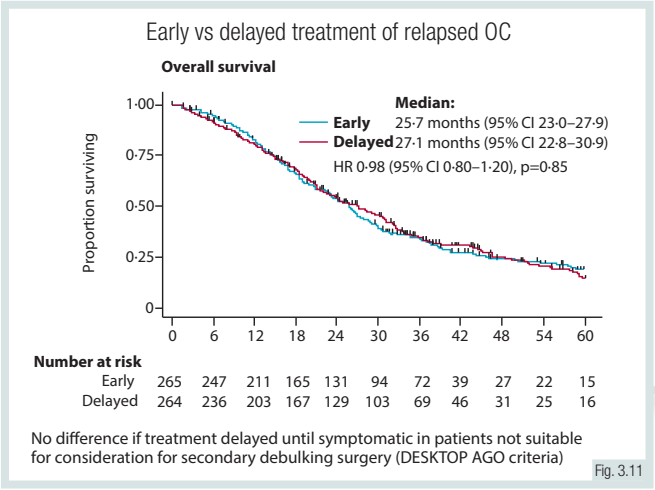
The DESKTOP III trial demonstrated a PFS and OS benefit in highly selected patients with OC at first relapse after a platinum-free interval of at least 6 months.

Secondary debulking surgery should only be considered in patients:

- who have had a complete resection at first surgery
- who have an ECOG (Eastern Cooperative Oncology Group) score of 0
- who present with ascites of <500 mL
- where complete surgical resection is achievable again



OS, overall survival.



CI, confidence interval; HR, hazard ratio; OC, ovarian cancer.

Follow-up should include a careful history (35% of patients have symptoms). Only ~4% have abnormal physical findings; however, patients find examination reassuring.

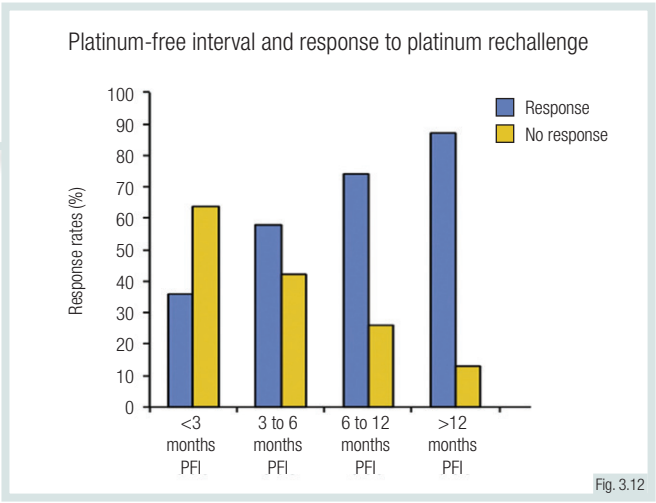
61% relapse with a rising CA125 level. Appropriate patients should have computed tomography (CT) imaging to determine if they are suitable candidates for secondary debulking surgery (see criteria above).

ChT treatment of asymptomatic patients with recurrent OC (ROC) has no impact on OS. CA125 level rises a median of 4 months prior to symptomatic recurrence.

Time from the last platinum-based treatment informs the likelihood of response to the next platinum-based therapy.

Extending the platinum-free interval by treating with non-platinum therapy (e.g. bevacizumab, taxanes, hormones) may help improve the likelihood of subsequent response.

Relapsing patients who have exhausted chemotherapeutic options may derive clinical benefit from hormonal therapies such as selective oestrogen-receptor modulators and aromatase inhibitors, although the body of evidence is limited.



PFI, platinum-free interval.

REVISION QUESTIONS

1. Which patients should be considered for secondary debulking surgery?
2. Define platinum-refractory/resistant OC.
3. How important is the platinum-free interval and what does it predict?

Management of patients with platinum-sensitive relapse

Platinum-sensitive (PS, 52%–61% overall response rate [ORR]) and partially platinum-sensitive (pPS, 27%–33% ORR) patients with OC should be re-treated with platinum-based ChT.

To mitigate hypersensitivity, substitute carboplatin with cisplatin or offer a desensitisation regimen.

Combinations of carboplatin with either gemcitabine (GC), pegylated liposomal doxorubicin (PLD) or paclitaxel improve PFS versus carboplatin alone, with additional benefit from bevacizumab.

OCEANS trial: in ROC bevacizumab improved PFS but not OS

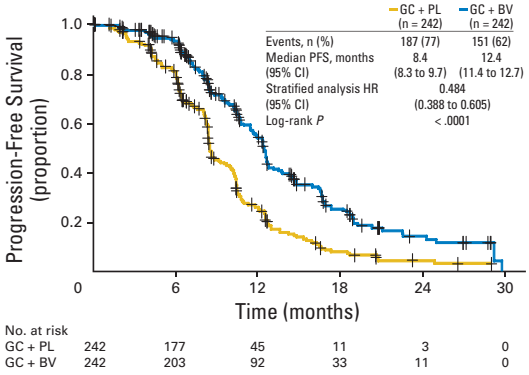


Fig. 3.13

BV, bevacizumab; CI, confidence interval; GC, gemcitabine and carboplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PL, placebo; ROC, relapsed ovarian cancer.

Effect of subsequent treatment on OS in ROC

AGO/NCIC/EORTC: OS

	C (n=178)	GC + PL (n=178)
Median OS, mo	17.3	18.0
HR (95% CI)	0.96 (0.75–1.23)	
Log-rank p value	0.7349	

OCEANS: 3rd interim OS analysis

	GC + PL (n=242)	GC + BV (n=242)
Median OS, mo	33.7	33.4
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank p value	0.7360	

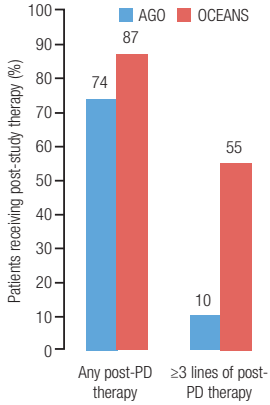


Fig. 3.14

BV, bevacizumab; C, carboplatin; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GC, gemcitabine and carboplatin; HR, hazard ratio; mo, months; NCIC, National Cancer Institute of Canada; OS, overall survival; PD, progressive disease; PL, placebo; ROC, relapsed ovarian cancer.

Olaparib maintenance prolongs PFS for patients with *BRCA*-mutated tumours following response to ChT for PS ROC.

Crossover (in SOLO-2, 38% patients in the placebo arm received a PARPi post-study) is likely to have influenced the OS results, and this was not significantly different between olaparib maintenance and placebo.

Many studies in high-grade serous OC (HGSC) fail to meet OS endpoints (e.g. GOG-0218, OCEANS, etc), mainly because of increasing numbers of post-progression therapies (see Fig. 3.14).

Comparison of OS data from the OCEANS trial (2012) and the original AGO study of GC in ROC (2006) shows that OS is related to the number of further lines of treatment after recurrence.

In fit patients, efforts should be made to identify or repeat lines of ChT. Clinical trials of new agents should be sought for such patients.

Additional maintenance strategies may further augment OS in selected populations.

Improvements in outcomes for maintenance PARPis in patients with *BRCA*m who have ROC

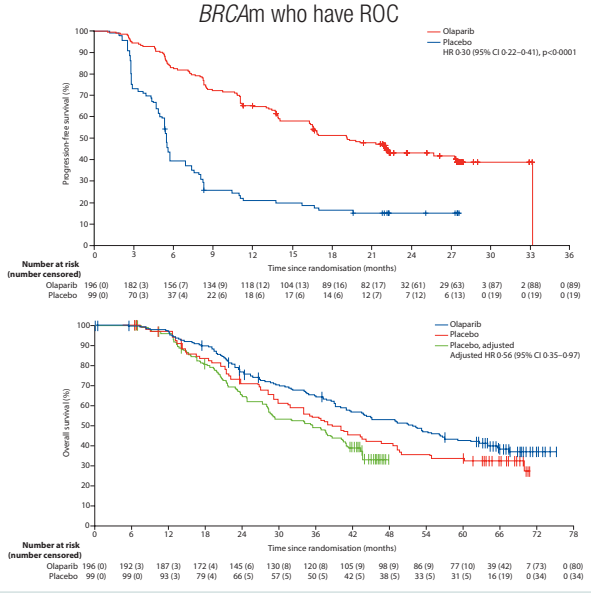


Fig. 3.15

BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; PARPi, poly (ADP-ribose) polymerase inhibitor; ROC, relapsed ovarian cancer.

REVISION QUESTIONS

1. How do subsequent lines of therapy impact on OS in patients with ROC?
2. What are the treatment options for patients who have had a hypersensitivity reaction to carboplatin?
3. What is the current indication for PARPis in ROC?

Use of PARPis in OC

Other PARPi maintenance trials have demonstrated PFS benefit over placebo in patients with OC following response to ChT for PS relapse, regardless of *BRCA* or HRD status.

Maintenance PARPis should be offered to all PS patients with relapsed HGSC who respond to ChT, provided they did not have a prior PARPi.

Careful monitoring of adverse effects is required to ensure optimal QoL for patients.

PARPis may have a degree of benefit in all patients regardless of *BRCA* or HRD status

Outcomes	NOVA	ARIEL 3
PFS *BRCA*m	21m vs 5.5m (HR = 0.27, 95% CI 0.08–0.88)	16.6m vs 5.4m (HR = 0.23, 95% CI 0.16–0.34)
PFS *BRCA*wt	9.3m vs 3.9m (HR = 0.45, 95% CI 0.34–0.61)	HRD+ 13.6m vs 5.4m (HR = 0.32, 95% CI 0.24–0.42) HRD- 6.7m vs 5.4m (HR = 0.58, 95% CI 0.40–0.85)
OS *BRCA*m / HRD+	35.6m vs 41.4m (HR = 1.29, 95% CI 0.86–1.95)	40.5 vs 47.8 (HR = 1.005, 95% CI 0.766–1.320
OS *BRCA*wt / HRD-	27.9m vs 27.9m (HR = 0.93, 95% CI 0.61–1.41)	N/A

Fig. 3.16

BRCAm, BRCA mutation; BRCAwt, BRCA wild-type; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; m, month; N/A, not applicable; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival.

Toxicities in specific PARPis

Adverse effect	Niraparib	Olaparib	Rucaparib
GI: nausea, bowel disturbance, anorexia, mucositis	●	●	●
Myelosuppression	●	●	●
Fatigue, myalgia	●	●	●
Palpitations, hypertension	●		
AST/ALT elevation	●		●
Increased serum creatinine		●	●

Fig. 3.17

ALT, alanine aminotransferase; AST, aspartate transaminase; GI, gastrointestinal; PARPi, poly (ADP-ribose) polymerase inhibitors.

Patients commencing PARPis develop tolerance to fatigue/nausea over 2–4 weeks. Close attention to haematological side effects is needed initially, with dose reductions as necessary.

Persistent elevations in serum creatinine and aspartate transaminase/alanine aminotransferase (AST/ALT) levels are observed in patients on certain PARPis. Those levels return to normal after stopping PARPis.

Close liaison with non-oncology medical teams is required to minimise unnecessary investigations of these biochemical changes.

Phase II trials of olaparib ± cediranib in bevacizumab/PARPi-naïve patients with PS ROC have shown that combination treatment is superior to olaparib alone.

Further information about the utility of PARPi/antiangiogenic maintenance therapy in relapse will be available when the phase III ICON9 study reports.

Olaparib ± cediranib versus ChT in PS ROC

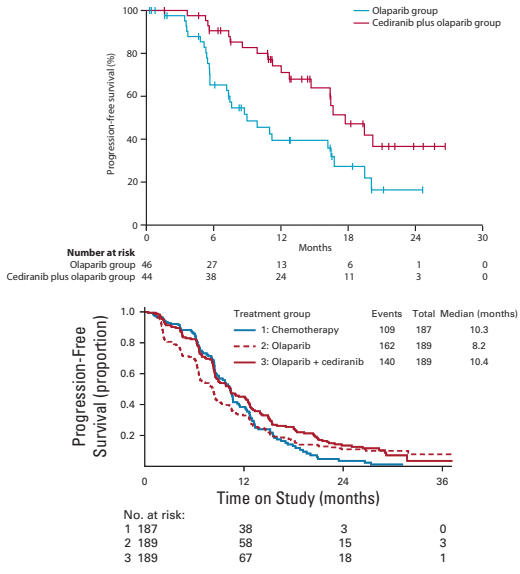


Fig. 3.18

ChT, chemotherapy; PS, platinum-sensitive; ROC, relapsed ovarian cancer.

REVISION QUESTIONS

1. What are the indications for PARPi therapy in ROC?
2. What are the most notable side effects of PARPi therapy?
3. Why has it been difficult to demonstrate an OS benefit for PARPi therapy in ROC?

Treatment of platinum-resistant ROC

Patients with platinum-resistant ROC have a poor prognosis (OS ~1 year); symptom control and QoL should be the primary focus.

Some patients, 3–6 months from last platinum treatment, benefit more from platinum-containing combinations than combinations without platinum (Lindemann et al, 2018).

Different scheduling, e.g. weekly paclitaxel and continuous low doses (metronomic ChT, e.g. cyclophosphamide), can be effective and improve outcomes.

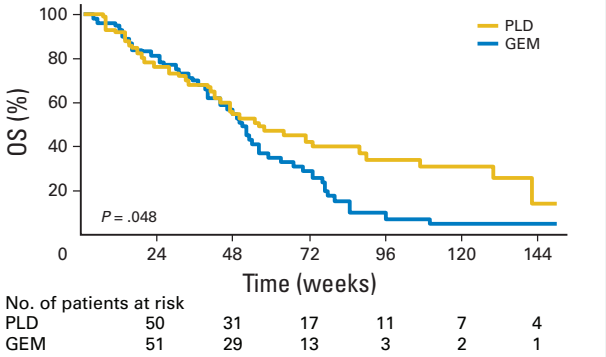


Fig. 3.19

ChT, chemotherapy; GEM; gemcitabine; OS, overall survival; PLD, pegylated liposomal doxorubicin.

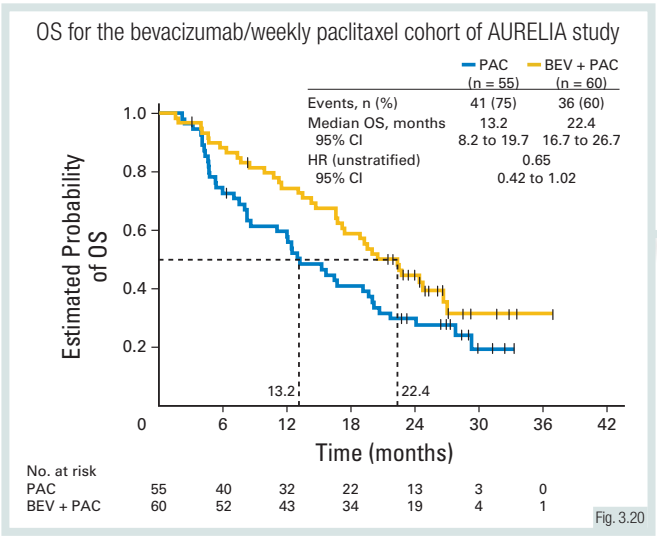


Fig. 3.20

BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; OS, overall survival; PAC, weekly paclitaxel.

Adding bevacizumab to ChT in patients with platinum-resistant ROC improves response and PFS but not OS.

In the AURELIA study, there was a more pronounced treatment effect on OS in patients who received weekly paclitaxel and bevacizumab (HR 0.65).

Intermittently dosed relacorilant, a selective glucocorticoid receptor modulator, has also shown promise in combination with nab-paclitaxel, increasing OS in a phase II study (NCT03776812), with phase III data expected.

Numerous phase III immunotherapy trials in OC have not shown any significant benefit; this is likely due to low neoantigen burden and T-cell dysfunction.

Pembrolizumab remains an option in mismatch repair-deficient (dMMR) tumours under tumour-agnostic treatment approval.

Trials combining immunotherapies with interleukin 2 (IL2), antibody–drug conjugates and vaccines are currently underway.

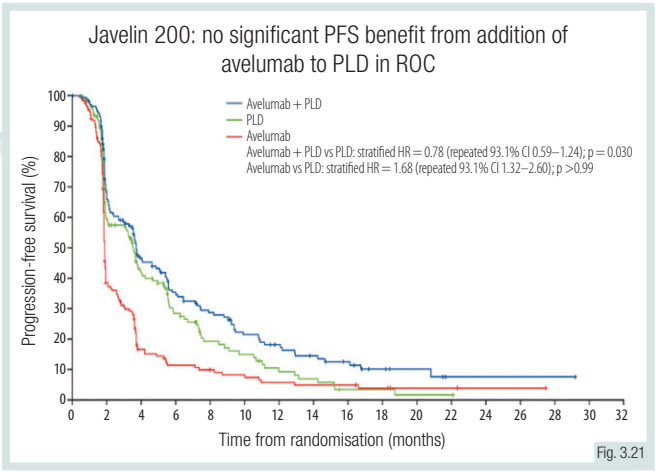


Fig. 3.21

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; ROC, relapsed ovarian cancer.

REVISION QUESTIONS

1. What are the aims of treatment in patients with platinum-resistant OC?
2. Does bevacizumab improve survival in platinum-resistant OC?
3. What are the indications for the use of immunotherapy in platinum-resistant OC?

Summary: Systemic treatment of ovarian cancer

- Adjuvant ChT (either 6 cycles TC ChT or carboplatin monotherapy) is generally recommended for FIGO stage I–IIB OC (except in low-grade stage IA)
- Surgery should be offered to all patients if at all possible, preferably prior to ChT (see Chapter 2)
- In high-risk groups, weekly TC ChT plus bevacizumab should be offered as adjuvant or neoadjuvant treatment
- Germline and somatic *BRCA1/2* and HRD testing are required to identify the patients likely to benefit from PARPi ± bevacizumab maintenance therapy
- Patients with PS and pPS ROC should be offered further platinum-based doublet ChT
- Patients with PS ROC who have responded to ChT should be offered maintenance PARPi, if they have not already received this first-line
- Platinum resistance is a spectrum; patients who relapse 4–6 months after the last platinum treatment may benefit from further platinum-based or combination treatments
- Best supportive care should be discussed with patients relapsing <3 months from the last platinum treatment, although some may benefit from single-agent ChT, such as weekly paclitaxel
- The addition of bevacizumab to weekly paclitaxel for bevacizumab-naïve patients in this setting prolongs PFS/OS
- Hormonal therapies such as selective oestrogen-receptor modulators and aromatase inhibitors can result in clinical benefit for patients with ROC and limited ChT options, although the body of evidence is limited

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4 Staging and surgical treatment of endometrial cancer

Epidemiology and pathology

Endometrial cancer (EC) is one of the most common cancers worldwide. In Europe, it represents the most common gynaecological malignancy.

The annual incidence in Europe is 8.9–26.2/100 000 women/year, with an annual mortality rate of 1.3–6.4/100 000 women/year. Across Europe, there are large differences in disease prevalence with higher rates in eastern and southern European countries.

Stage I EC 5-year survival varies from 77.6% to 89.6%, whereas for stage III the survival rate is 49%–57%.

5-year prevalence of endometrial cancer in European countries

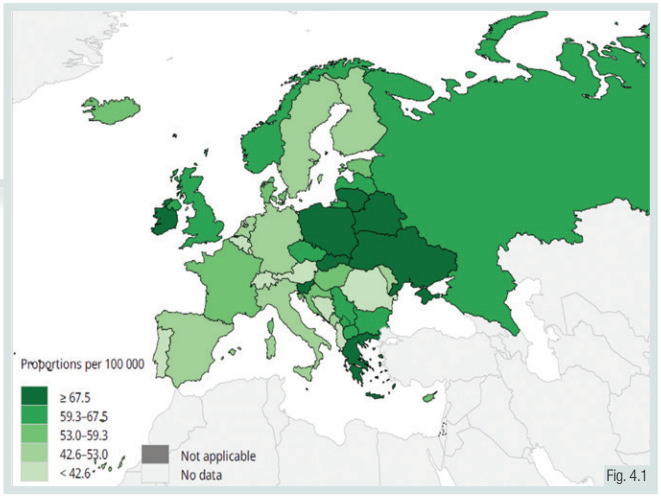


Fig. 4.1

Low-grade endometrioid tumour (left), high-grade carcinosarcoma (right)

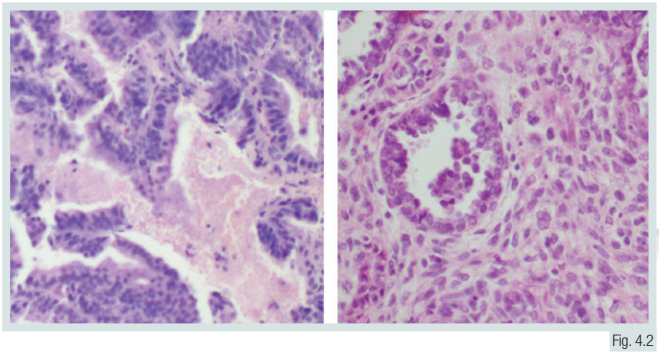


Fig. 4.2

The 5th edition of the World Health Organization (WHO) classification of Female Genital Tumours differentiates: endometrioid carcinoma (adenocarcinoma, adenocarcinoma variants), mucinous, serous and clear cell adenocarcinoma, undifferentiated carcinoma and neuroendocrine tumours.

Currently, only low-grade (grade 1 and 2) and high-grade differentiation are used.

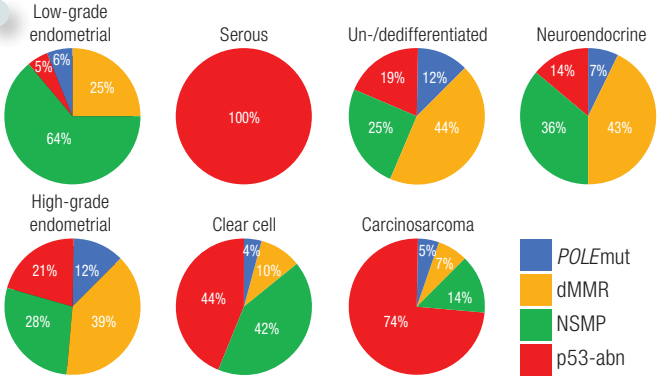
Lymphovascular space invasion (LVSI) is now categorised as: absent, focal or substantial.

Based on The Cancer Genome Atlas (TCGA), a molecular classification of tumours has been proposed:
(1) polymerase epsilon (*POLE*)-ultramutated (*POLE*mut);
(2) microsatellite instability (MSI), in some papers presented as mismatch repair-deficient (dMMR);
(3) copy number-high – p53;
(4) no specific molecular profile (NSMP).

Immunohistochemistry of p53 and MMR should be used to assess proteins MLH1, PMS2, MSH6, MSH2, to identify patients with Lynch syndrome.

Molecular analysis of *POLE* should be used in ECs, especially in high-grade tumours. Further prospective data is needed to evaluate the significance of molecular classification.

Distribution of TCGA molecular groups according to histological types



dMMR, mismatch repair-deficient; NSMP, no specific molecular profile; p53-abn, p53 abnormal; POLEmut, POLE ultramutated; TGCA, The Cancer Genome Atlas.

Fig. 4.3

REVISION QUESTIONS

1. Is EC a common cancer in Europe?
2. What is the mortality rate of EC in Europe?
3. Name four types of endometrial tumours based on TCGA classification.

Examination and prognostic factors

There are several known risk factors for EC: obesity, diabetes mellitus, nulliparity, polycystic ovary syndrome and tamoxifen administration.

Lynch syndrome/hereditary non-polyposis colorectal cancer is a confirmed risk factor, while use of oral contraception, a higher number of deliveries and smoking are protective.

The International Federation of Gynecology and Obstetrics (FIGO) staging of EC (updated in 2023) is currently used, which includes molecular stratification.

FIGO staging of endometrial cancer (2023)*

Stage	Description
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
Stage III	Local and/or regional spread of the tumour of any histological subtype
IIIA	Invasion of uterine serosa, adnexa or both by direct extension or metastasis
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain or bone

Fig. 4.4

*This is an abridged version of the 2023 FIGO staging. Please find the full version in Appendix 2: FIGO Ovarian, Fallopian Tube and Peritoneal Cancer Staging System and Corresponding TNM on page 75.

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; TNM; tumour, node, metastasis.

Ultrasound image of endometrial cancer stage IA

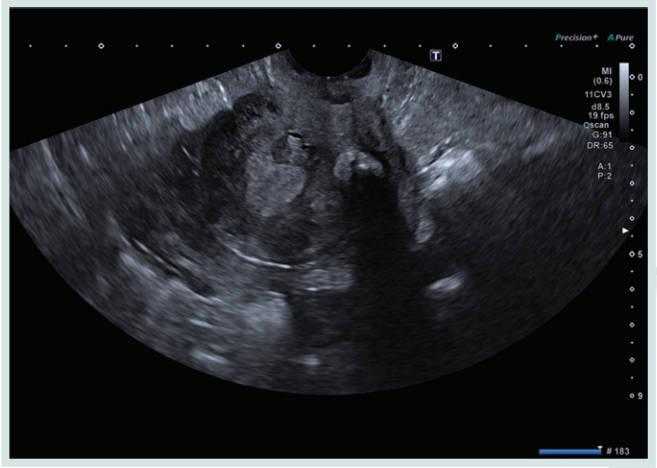


Fig. 4.5

Most cases of EC present as abnormal vaginal bleeding or discharge.

Clinical and ultrasound examination (transvaginal ultrasound [TVUS]) should be the first steps of management. Magnetic resonance imaging (MRI) is an alternative to TVUS.

Histopathological confirmation is best performed by dilatation and curettage (D&C) with hysteroscopic guidance, followed by D&C alone and then pipelle aspiration.

Several prognostic factors that have an impact on survival outcome have been described: myometrial invasion, lymph node (LN) involvement, histological type, histological grade, LVSI and tumour diameter >2 cm.

Evaluation of molecular classification determines the FIGO stage and may influence adjuvant therapy. *POLE*mut tumours are associated with a favourable prognosis and allow de-escalation of postoperative radiotherapy. Conversely, p53-abn tumours exhibit a worse prognosis.

Addition of molecular classification

Stage designation	Molecular findings in patients with early endometrial cancer (stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLE*mut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53\text{-}abn}$	p53-abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Fig. 4.6

LVSI, lymphovascular space invasion; p53-abn, p53 abnormal; POLEmut, polymerase epsilon ultramutated.

REVISION QUESTIONS

1. What risk factors play a role in the development of EC?
2. How do you verify a suspicion of EC?
3. What is the role of *POLE* mutation?

Surgical treatment

For early-stage cancer (I, II) a total, simple hysterectomy with bilateral salpingo-oophorectomy and sentinel LN (SLN) mapping (SLNM) is a standard procedure.

Based on prospective trials, minimally invasive surgery (MIS) is the preferred route for low-, intermediate- and also high-risk patients.

Extrauterine progression of the disease is a contraindication for MIS; lymphadenopathy is a contraindication for systemic lymphadenectomy (LND). Intraperitoneal spillage should be avoided.

OS based on randomly assigned treatment groups in the LAP2 study

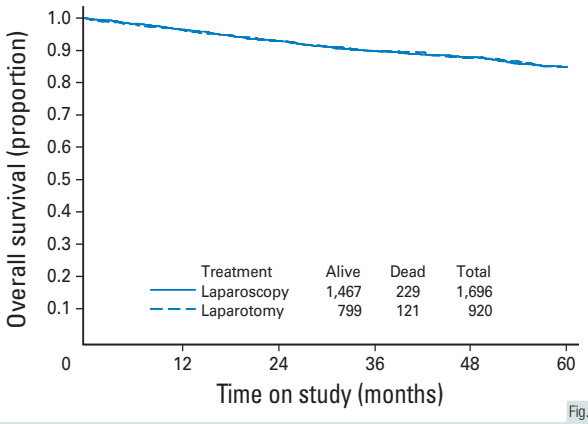


Fig. 4.7

OS, overall survival.

Indocyanine green SLNM

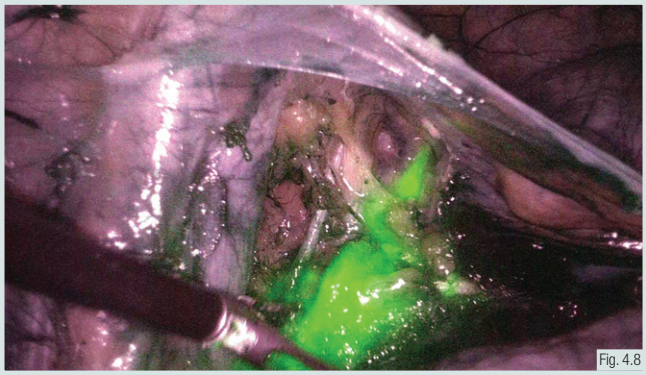


Fig. 4.8

SLNM, sentinel lymph node mapping.

SLNM-only is an alternative to systemic LND.

For the detection of SLNs, a combination of technetium and patent blue is used; indocyanine green injected intracervically shows a better rate of detection.

Para-aortic lymphadenectomy (PALND) during systemic LND is recommended, but the effect on survival of PALND staging versus SLNM is currently under investigation.

Intraoperative frozen-section examination of myometrial invasion and SLNs is not recommended; only bulky LNs should be examined.

Ultrastaging of SLNs is recommended. Micrometastatic nodal involvement worsens the prognosis, while isolated tumour cells do not.

In serous carcinoma, carcinosarcoma and undifferentiated carcinoma, an infracolic omentectomy should be included for staging reasons.

Evaluation of positivity of SLNs and non-SLNs

Author	Study population	Metastasis	
		In SLN (%)	Not in SLN, but in other lymph node (i.e. false-negative SLN)
Including grade 1 and 2			
Cusimano et al. 2021	30	3 (10)	0
Stephens et al. 2020	323	58 (18)	0
Ye et al. 2019	106	3 (3)	0
Including grade 1–3			
Backes et al. 2019	204	32 (16)	2
Bogani et al. 2020	62	9 (15)	0
Cusimano et al. 2021	156	24 (15)	3
Holloway et al. 2016	119	35 (29)	1
Rossi et al. 2017	340	35 (10)	1
Xue et al. 2021	130	7 (5)	2
Ye et al. 2019	131	4 (3)	4

Fig. 4.9

Note that the diagnostic value was calculated twice: for studies including grade 1–2 endometrial cancer, and for studies including grade 1, 2 and 3 endometrial cancer.

SLN, sentinel lymph node.

REVISION QUESTIONS

1. What is the contraindication for MIS?
2. Which compounds are being used for SLNM?
3. Is infracolic omentectomy indicated in EC surgery?

Summary: Staging and surgical treatment of endometrial cancer

- EC is one of the most common cancers worldwide with a low mortality when diagnosed at early stage
- With the emergence of new data, the molecular classification of tumours and immunohistochemistry play an increasingly important role in risk stratification and are recommended for optimal management
- Ultrasound imaging and biopsy precede any therapeutic decision
- MIS is an integral part of early-stage EC treatment
- SLNM is an integral part of surgical staging

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Image sources: **Fig. 4.1.** Ferlay J, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer, 2020. Available from: https://gco.iarc.fr/today [accessed 22 May 2024].; **4.2.** courtesy of Jana Drozenova, Dept. of Pathology, University Hospital Kralovske Vinohrady, Czech Republic; **4.3.** Santoro A, et al. Cancers (Basel) 2021;13:2623; **4.4, 4.6.** adapted from Berek JS, et al. J Gynecol Oncol 2023;34:e85; **4.7.** Walker JL, et al. J Clin Oncol 2012;30:695-700; **4.9.** adapted from Burg LC, et al. J Gynecol Oncol 2022;33:e66. All other figures courtesy of the authors.

5 Non-surgical treatment of endometrial cancer

Molecular classification

The International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial cancer (EC) was updated in 2023.

The new staging incorporates molecular classifications.

Using somatic mutations, copy number alterations and microsatellite instability (MSI), The Cancer Genome Atlas (TCGA) identified four molecular subtypes: polymerase epsilon (*POLE*, [ultramutated], *POLE*mut), microsatellite instability-hypermutated (MSI-H), copy number-low (endometrioid) and copy number-high (serous-like)/ p53-abnormal (p53-abn).

Molecular classification of endometrial cancer

Subgroup	Incidence	Cancer mortality
TP53/serous-like/copy-number altered	8%	19%
No specific molecular profile/low copy number variant/copy-number stable	49%	5%
MSI+/MMR-deficient	39%	7.6%
POLE ultramutated	4%	2.6%

TCGA: Whole-genome sequencing, exome sequencing, MSI assays, copy number and proteomics to classify 373 endometrial cancers (307 endometrioid, 53 serous and 13 mixed histology cases).

MMR, mismatch repair; MSI, microsatellite instability; POLE, polymerase epsilon; TCGA, The Cancer Genome Atlas.

Fig. 5.1

Endometrial cancer: molecular subtypes

POLE ultramutated ~4% ECs	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Best prognosis
MSI hypermutated ~39% ECs	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations
Copy number-low ~49% ECs	• High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression
Copy number-high ~9% ECs	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1*, and *PTEN* mutations • Worst prognosis

EC, endometrial cancer; MSI, microsatellite instability; MSS, microsatellite stable; POLE, polymerase epsilon; PTEN, phosphatase and tensin homologue.

Fig. 5.2

30%–40% of endometrioid tumours are MSI-H.

Lynch syndrome-associated ECs are MSI-H.

Most serous (copy number-high) ECs have *TP53* mutations.

The addition of molecular subtypes to staging criteria allows a better prediction of prognosis.

*POLE*mut ECs have the best prognosis and research focusing on treatment de-escalation is needed.

Copy number-high tumours have the worst prognosis.

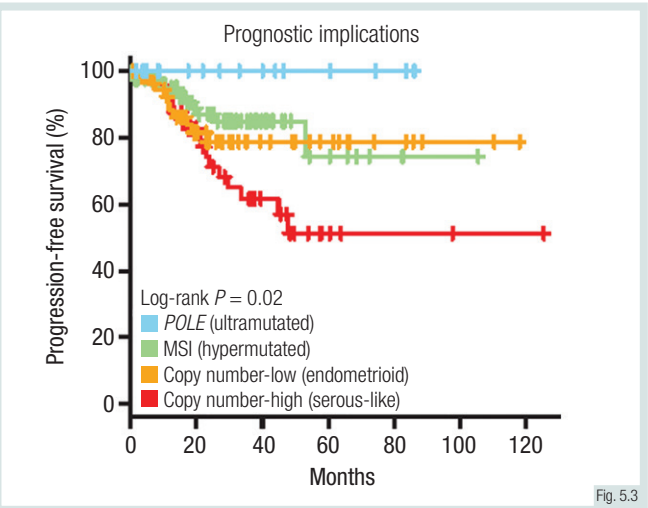


Fig. 5.3

MSI, microsatellite instability; POLE, polymerase epsilon.

REVISION QUESTIONS

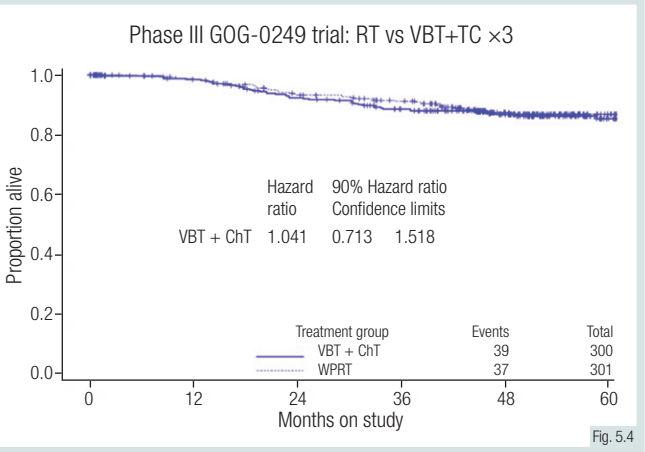
1. What is the molecular classification of a newly diagnosed patient with proficient mismatch repair (pMMR) protein and *TP53* mutation?
2. Which molecular classification has the best prognosis?
3. In a woman with a family history of Lynch syndrome who develops EC, what is the most likely molecular classification?

Adjuvant therapy

In patients with high-intermediate-risk disease (e.g. stage I/II, grade 2/3, lymphovascular space invasion [LVSI]-positive) there is no difference in benefit between chemotherapy (ChT) with vaginal brachytherapy and pelvic radiotherapy (RT).

In patients with MMR-deficient (dMMR) tumours, the addition of ChT to RT did not significantly improve overall survival (OS) or recurrence-free survival (RFS) benefit.

Initial observations from TCGA suggest that *POLE*mut tumours do not recur.



ChT, chemotherapy; RT, radiotherapy; TC, carboplatin and paclitaxel; VBT, vaginal brachytherapy; WPRT, whole-pelvis radiotherapy.

Adjuvant CRT vs RT alone in HREC (PORTEC-3 trial)

	dMMR		pMMR*	
	+RT	+CRT	+RT	+CRT
5-year OS	84.0%	78.6%	87.6%	89.3%
	HR 1.33 (95% CI, 0.64-2.75) p = 0.445		HR 0.68 (95% CI, 0.26-1.77) p = 0.434	
5-year RFS	75.5%	68.0%	67.7%	79.7%
	HR 1.29 (95% CI, 0.68-2.45) p = 0.429		HR 0.68 (95% CI, 0.36-1.30) p = 0.246	

Fig. 5.5

The addition of ChT to RT in patients with dMMR HREC did not produce a significant OS or RFS benefit.

* No specific molecular profile identified after assessment of MMR status, *POLE*mut status and p53 status.

ChT, chemotherapy; CI, confidence interval; CRT, chemoradiotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; HREC, high-risk endometrial cancer; OS, overall survival; pMMR, mismatch repair-proficient; POLEmut, polymerase epsilon ultramutated; RFS, recurrence-free survival; RT, radiotherapy.

For patients with no specific molecular profile (NSMP)-EC and intermediate risk factors, adjuvant brachytherapy provides excellent vaginal control and high survival rates.

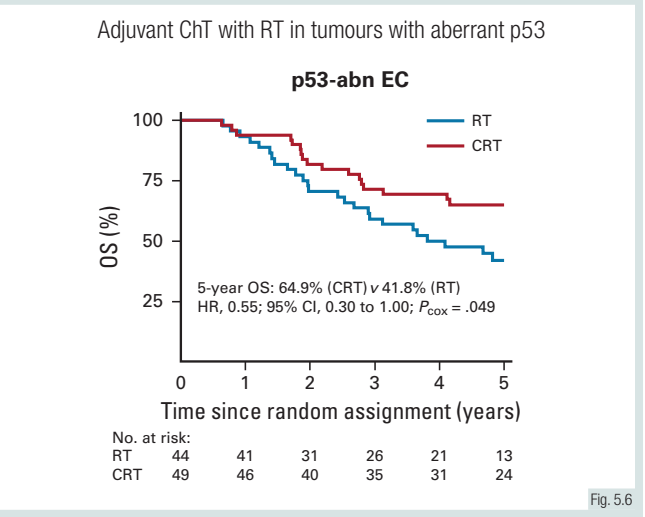
Adjuvant therapy, however, does not yield a higher OS. Therefore, no adjuvant therapy remains an option.

Further investigation needs to be done to evaluate the role of immunotherapy in the adjuvant setting.

Generally, dMMR tumours are less responsive to ChT than pMMR ECs.

Tumours with *TP53* mutations (~70% serous, 23% endometrioid, 7% other/mixed [in the PORTEC-3 trial]) are more likely to respond to adjuvant chemoradiotherapy (CRT) than other ECs.

ChT plus RT does not offer any additional benefit over RT alone for NSMP tumours.



CI, confidence interval; ChT, chemotherapy; CRT, chemoradiotherapy; EC, endometrial cancer; HR, hazard ratio; OS, overall survival; p53-abn, p53 abnormal; RT, radiotherapy.

REVISION QUESTIONS

1. What type of adjuvant therapy is recommended for high-intermediate-risk EC?
2. In a patient with a stage IB uterine serous cancer which has a *TP53* mutation, what would be your recommended adjuvant therapy?
3. Does adjuvant therapy for high-intermediate-risk EC improve OS?

First-line systemic treatment for recurrent or metastatic EC

Ensure proper staging is performed to enable patients with local recurrence to be offered potentially curative surgery/RT.

The choice between first-line ChT or hormonal treatment should be made on a case-by-case basis.

Decisions should consider grade, hormone receptor expression, histology and patient comorbidities.

Factors to consider when choosing between ChT and hormonal therapy for recurrent/metastatic EC

Hormonal agents	Chemotherapy
• Elderly patients • Asymptomatic • Grade 1 endometrioid • Hormone receptor-positive	• Rapidly progressing • Symptomatic • High grade • p53-abn • Non-endometrioid histology • Hormone receptor-negative

ChT, chemotherapy; EC, endometrial cancer; p53-abn, p53 abnormal. Fig. 5.7

GOG-0209 randomised phase III trial of doublet vs triplet as first-line ChT

	TC	TAP	
ORR	52%	52%	
PFS	13 months	14 months	HR 1.032
OS	37 months	41 months	HR 1.002
TRAEs	More neutropenia	More thrombopenia, N/V/diarrhoea	$p < 0.001$

Fig. 5.8

ChT, chemotherapy; HR, hazard ratio; N/V, nausea/vomiting; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TAP; cisplatin, doxorubicin and paclitaxel; TC, carboplatin and paclitaxel; TRAE, treatment-related adverse event.

The phase III GOG-0209 trial compared the triplet (cisplatin, doxorubicin and paclitaxel [TAP]) with the carboplatin and paclitaxel (TC) doublet in stage III or IV EC (N=865).

There was no difference in efficacy; however, the triplet was more toxic. Thus, TC was established as the standard of care for first-line metastatic EC.

Further investigation is needed to evaluate the role of ChT in the relapse setting, with respect to each of the four molecular subclassifications.

Overall, the most studied hormonal agents are progestogens (megestrol acetate 160 mg/day or medroxyprogesterone 200 mg/day) with a response rate (RR) close to 30%.

Other agents such as aromatase inhibitors and gonadotropin-releasing hormone (GnRH) analogues have also shown activity in metastatic EC.

Counterintuitively, tamoxifen also has activity in metastatic EC, either alone (RR: 10%–53%) or in combination with progestogens (RR: 19%–58%).

Activity of hormonal agents in hormone receptor-positive EC

Study	Meta-analysis 2017 N=184	Megestrol acetate N=35 NCT00910091	Anastrozole N=82 PARAGON trial – ANZGOG 0903
ORR	26.6%	35%	7%
Median PFS		9 months	3.2 months

EC, endometrial cancer; N, number of patients; ORR, objective response rate; PFS, progression-free survival. Fig. 5.9

REVISION QUESTIONS

1. Which ChT would you propose in the first-line setting for a patient with disease recurrence 2 years after local treatment?
2. Which treatment would you propose in an elderly patient relapsing with oestrogen receptor (ER)-positive EC?
3. What is the most studied hormonal regimen for EC?

Second-line treatment options post-platinum

Previously, second-line ChT (doxorubicin or paclitaxel) resulted in a median progression-free survival (PFS) of 3–4 months. However, the landscape has significantly changed in recent years.

Up to 30% of ECs are dMMR. This defect in MMR results in high tumour mutation burden and increased infiltration by CD8+ cytotoxic T cells. As with other dMMR cancers, objective responses to single immune checkpoint inhibitors (ICIs) are observed in 40% to 50% of dMMR ECs for prolonged durations.

The ICIs dostarlimab and pembrolizumab have been approved for use in dMMR EC progressing after platinum, thus providing an active ChT-free option for these patients.

Phase I/II trials of single-agent ICIs in dMMR EC that led to approvals

	KEYNOTE-158 NCT02628067	Garnet NCT02715284
N		129
ICI	Pembrolizumab	Dostarlimab
ORR	48%	44%
PFS	13 months	>12 months

Fig. 5.10

dMMR, mismatch repair deficient; EC, endometrial cancer; ICI, immune checkpoint inhibitor; N, number of patients; ORR, objective response rate; PFS, progression-free survival.

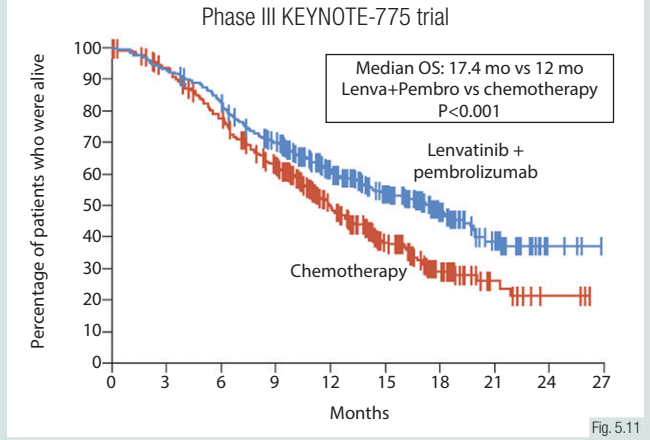


Fig. 5.11

Lenva, lenvatinib; mo, months; OS, overall survival; Pembro, pembrolizumab.

Single-agent ICIs are less active in pMMR ECs relapsing post-platinum.

A phase III randomised trial in patients with EC who had disease progression after platinum, compared pembrolizumab plus lenvatinib to ChT (investigator's choice of doxorubicin or weekly paclitaxel). Pembrolizumab plus lenvatinib improved RRs (35% vs 15%), PFS and OS in pMMR EC and the all-comer population (including dMMR EC).

The combination comes with increased toxicity: 88.9% grade 3 adverse events for patients on lenvatinib plus pembrolizumab (38% G3 hypertension) versus 72.7% for ChT patients.

ChT with alternate antiangiogenics may be useful and less toxic in the relapse setting for patients with p53-abn EC.

Results are awaited from the COPELIA study, which randomised patients with relapsed EC to weekly paclitaxel versus weekly paclitaxel with cediranib versus cediranib plus olaparib.

Platinum rechallenge may be considered especially in patients with a prolonged platinum-free interval.

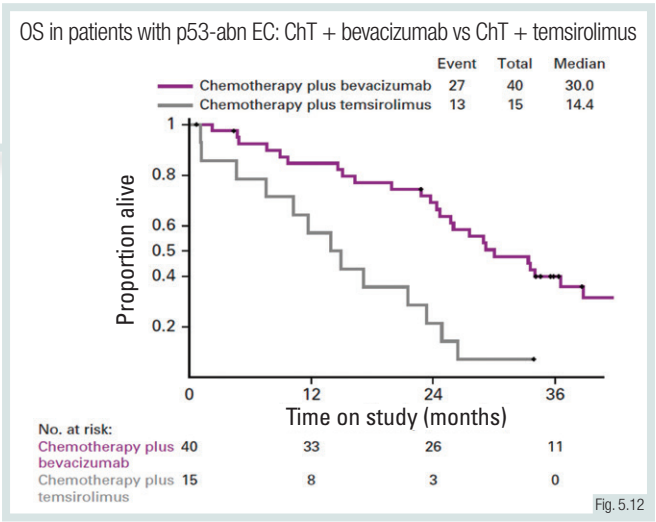


Fig. 5.12

ChT, chemotherapy; EC, endometrial cancer; OS; overall survival; p53-abn, p53-abnormal.

REVISION QUESTIONS

1. What treatment options could you discuss for a patient with dMMR EC progressing 1 year after first-line ChT (TC)?
2. What treatment would you propose for a patient with pMMR EC progressing after first-line ChT (TC)?
3. What is the role of ICIs in relapsed EC, both dMMR and pMMR?

Novel therapeutic approaches

The addition of an ICI (dostarlimab or pembrolizumab) to ChT (TC) has been shown to improve survival in two phase III randomised trials. Benefit was greatest in patients with dMMR tumours, resulting in approval by the Food and Drug Administration and European Medicines Agency for dostarlimab in the dMMR subset.

Additionally, two of these trials have included a further randomisation to poly (ADP-ribose) polymerase (PARP) inhibition as maintenance in biomarker-unselected EC.

ChT-free options for first-line relapsed/metastatic EC?

- The LEAP trial comparing ChT (TC) versus lenvatinib plus pembrolizumab in the first line, regardless of MMR status, has completed recruitment.
- In dMMR EC, two trials are currently comparing single-agent ICIs (pembrolizumab or dostarlimab) to standard first-line ChT (TC).

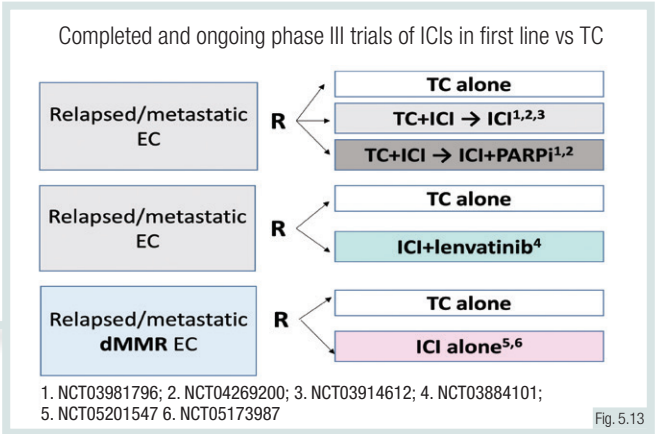


Fig. 5.13

dMMR, mismatch repair deficient; EC, endometrial cancer; ICI, immune checkpoint inhibitor; PARPi, poly (ADP-ribose) polymerase inhibitor; R, randomisation; TC, carboplatin and paclitaxel.

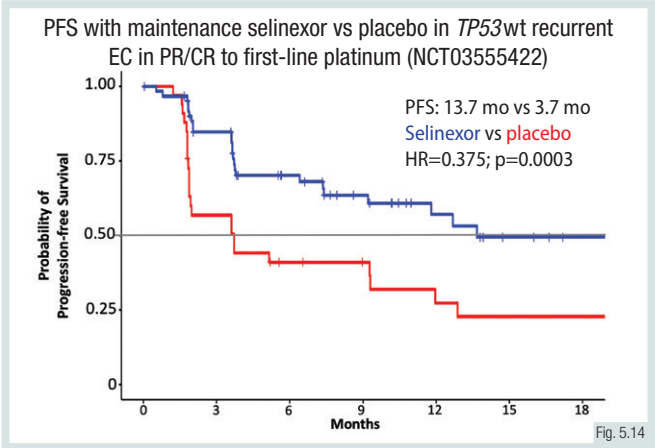


Fig. 5.14

CR, complete response; EC, endometrial cancer; HR, hazard ratio; mo, months; PFS, progression-free survival; PR, partial response; wt, wild-type.

Selinexor inhibits nuclear export of the wild-type *TP53* tumour suppressor gene.

In patients with advanced/recurrent EC, who had achieved a partial or complete response to first-line TC, maintenance selinexor improved PFS compared with placebo in the *TP53* wild-type cohort.

A confirmatory trial dedicated to *TP53* wild-type EC is currently recruiting (NCT05611931).

Human epidermal growth factor receptor 2 (HER2) amplification is described in 30% of serous ECs. The addition of trastuzumab to first-line TC significantly increased both PFS and OS in HER2-amplified serous EC.

The cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, palbociclib, ribociclib and abemaciclib, have been combined with aromatase inhibition in ER-positive EC with encouraging early signals of activity, mainly in low-grade ER-positive EC.

Non-endometrioid or p53-abn EC is frequently hormone receptor-negative and other approaches are currently under investigation, including PARP inhibition.

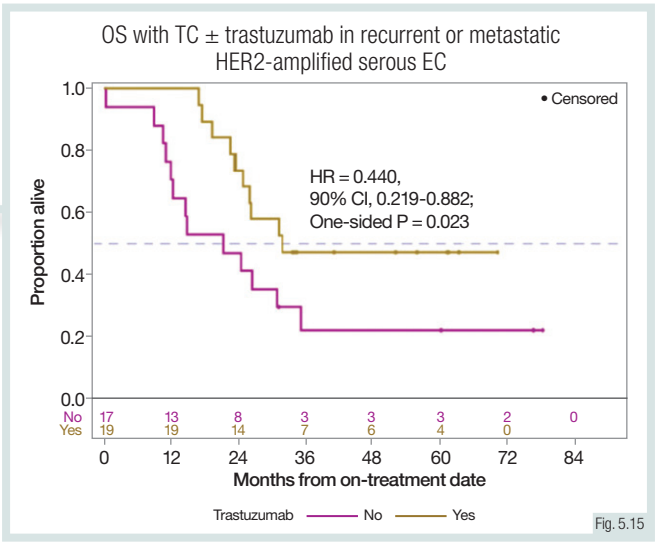


Fig. 5.15

CI, confidence interval; EC, endometrial cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; TC, carboplatin and paclitaxel.

REVISION QUESTIONS

1. Which ICIs have shown benefit when combined with first-line TC?
2. Who benefitted the most from the addition of an ICI in the two first-line trials?
3. Give two examples of targeted therapies under investigation in relapsed EC which have shown positive results in randomised clinical trials.

Summary: Non-surgical treatment of endometrial cancer

- Molecular classification should be incorporated into EC staging
- *POLE*mut ECs have a better prognosis than other molecular classifications
- dMMR ECs are less likely to respond to ChT in the adjuvant setting
- ChT is more active in women with p53-abn EC
- The standard-of-care ChT for relapsed/metastatic EC is TC
- Hormonal therapy is an alternative in hormone receptor-positive EC, especially in slow growing, low-grade endometrioid tumours
- In patients progressing after platinum ChT, the combination of pembrolizumab and lenvatinib can be proposed
- Additionally, in patients with dMMR EC progressing after platinum, another option is single-agent ICI (pembrolizumab or dostarlimab)
- Two randomised phase III trials investigating the combination of an ICI with first-line ChT (TC) have shown improvement in survival

Further Reading

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Image sources: **Fig. 5.1, 5.2.** courtesy of the authors, source: Cosgrove CM, et al. Gynecol Oncol 2018;148:174-180; **5.3.** Cancer Genome Atlas Research Network; Kandoth C, et al. Nature 2013;497:67-73; **5.4.** Randall ME, et al. J Clin Oncol 2019;37:1810-1818; **5.6.** León-Castillo A, et al. J Clin Oncol 2020; 38:3388-3397; **5.11.** Makker V, et al. N Engl J Med 2022;386:437-448; **5.12.** Thiel KW, et al. J Clin Oncol 2022;40:3289-3300; **5.14.** courtesy of Ignace Vergote; **5.15.** Fader AN, et al. Clin Cancer Res 2020;26:3928-3935. All other figures courtesy of the authors.

6 Staging and surgical treatment of cervical cancer

Pathological staging of cervical cancer

Stage IA cervical cancer (CC) is an invasive carcinoma with a maximal depth of stromal invasion of 5.0 mm.

There are two substages according to the depth of stromal invasion: <3.0 mm (stage IA1) and 3.0–5.0 mm (stage IA2).

Stage IB is a tumour limited to the cervix and greater than stage IA. It has three substages, according to the greatest dimension: <2 cm (stage IB1), 2–4 cm (stage IB2) and >4 cm (stage IB3).

Stage I cervical cancer

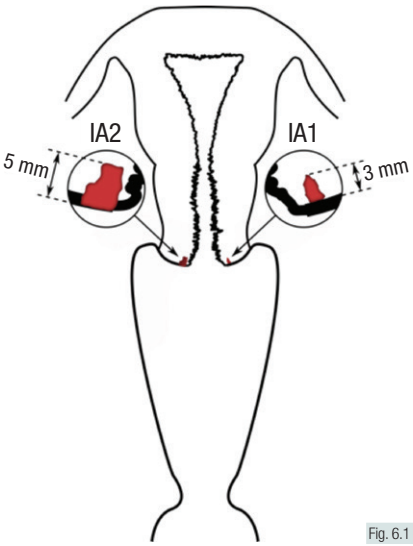


Fig. 6.1

Stage II cervical cancer

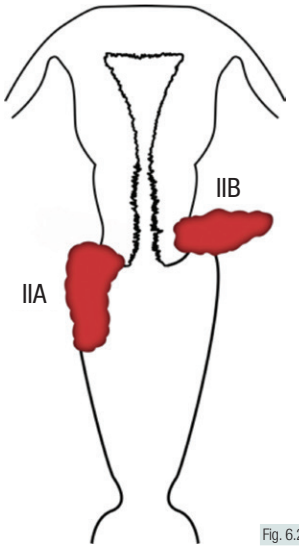


Fig. 6.2

A stage II tumour invades either the proximal two-thirds of the vagina, with the greatest dimension of 4 cm (stage IIA1) or larger (stage IIA2), or to the parametria (stage IIB).

A stage IIIA tumour invades the lower third of the vagina. Stage IIIB either reaches the pelvic wall or causes hydronephrosis or a non-functioning kidney.

A stage IV tumour invades either the full wall thickness of the bladder or rectum (stage IVA) or it extends beyond the pelvis (stage IVB).

Involvement of pelvic and/or para-aortic lymph nodes (LNs) is classified as stage IIIC.

Pelvic nodes (N1) include the paracervical, parametrial, internal iliac, obturator, common iliac, external iliac and presacral LNs. Para-aortic nodes (N2) include the inferior (up to the inferior mesenteric artery) and superior (up to the renal veins) mesenteric LNs.

Involvement of inguinal LNs is considered distant metastasis (M1).

Involvement of regional LNs (N1-N2) is classified as FIGO stage IIIC-IVB.

FIGO stages	TNM categories T	N	M
IIIB	T3b	N0	M0
IIIC1	TX, T1–T3	N1	M0
IIIC2	TX, T1–T3	N2	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; TNM, tumour, node, metastasis.

Fig. 6.3

REVISION QUESTIONS

1. What is the difference between stage IA and stage IB CC?
2. What is the criterion for distinction between stages IA1 and IA2?
3. Are para-aortic LNs considered regional LNs in CC?

Clinical and surgical staging, prognostic factors

In pretreatment (clinical) staging, mandatory work-up includes gynaecological examination, biopsy and imaging.

Pelvic magnetic resonance imaging (MRI) or expert ultrasound (US) are the preferred imaging modalities to assess the pelvic tumour extent and guide treatment options in early stages. Cystoscopy, rectoscopy or evaluation under general anaesthesia are not routinely recommended.

In locally advanced stages, positron emission tomography–computed tomography (PET–CT), CT or whole body (WB)-MRI should be performed to assess for distant spread.

Recommended clinical staging

Pelvic assessment	Distant assessment
Gynaecological examination	PET–CT or CT or WB-MRI
Pelvic MRI or expert US	

Fig. 6.4

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound; WB, whole body.

Main risk factors for disease-free survival in early-stage disease

Predictor		β	SE(β)	HR (95% CI)	P-value	Risk points (max. 100)
Histotype	Squamous cell			Reference		0
	Adenocarcinoma	0.342	0.116	1.408 (1.120; 1.771)	0.003	7
	Adenosquamous	0.598	0.164	1.819 (1.317; 2.513)	< 0.001	11
	Neuroendocrine	1.741	0.246	5.704 (3.514; 9.260)	< 0.001	33
	Other	1.145	0.270	3.144 (1.848; 5.349)	< 0.001	22
Tumour diameter	<0.5 cm			Reference		0
	0.5–1.99 cm	0.501	0.237	1.651 (1.035; 2.634)	0.035	10
	2–3.99 cm	1.115	0.236	3.051 (1.915; 4.858)	< 0.001	21
	≥4 cm	1.556	0.245	4.738 (2.925; 7.674)	< 0.001	30
Grade	1			Reference		0
	2	0.260	0.214	1.297 (0.852; 1.976)	0.235	5
	3	0.457	0.247	1.579 (0.970; 2.570)	0.085	9
Positive pelvic LN	0/not assessed			Reference		0
	1	0.255	0.154	1.291 (0.953; 1.748)	0.098	5
	2	0.482	0.170	1.619 (1.158; 2.264)	0.005	9
	≥3	0.939	0.144	2.557 (1.927; 3.394)	< 0.001	18
LVSI	No/not assessed			Reference		0
	Yes	0.538	0.106	1.713 (1.390; 2.111)	< 0.001	10

Fig. 6.5

β, beta coefficient; CI, confidence interval; HR, hazard ratio; LN, lymph node; LVSI, lymphovascular space invasion; SE, standard error.

LN involvement is one of the most significant prognostic parameters in the early stages of CC. Oncological outcome is related to the number of positive pelvic LNs.

Additional prognostic parameters in early stages include: tumour size, tumour stage, lymphovascular space invasion (LVSI), depth of stromal invasion, tumour-free distance (TFD: width of free stroma between tumour and parametria) and histological type (worse prognosis for adenosquamous carcinomas and non-human papillomavirus [HPV]-associated adenocarcinomas).

Involvement of para-aortic LNs is associated with significantly worse prognosis.

The prevalence of LN involvement increases with the stage of the disease.

Assessment of sentinel LNs (SLNs) by pathological ultrastaging substantially increases the accuracy of LN staging since it can detect additional macrometastases (>2 mm) and almost all micrometastases (0.2–2 mm).

Presence of micrometastases in SLNs is associated with similarly worse prognosis as for macrometastases. Presence of isolated tumour cells (ITCs, <0.2 mm) is generally considered a negative prognostic factor, although its prognostic significance cannot be proved prospectively.

Lymph node positivity according to FIGO stage

	% within clinical stages				p value[1]
	IA	IB1	IB2	IIA/IIB	
Final lymph node status (SLN ultrastaging & pelvic nSLN)					
Macrometastasis	9.1%[a]	19.5%[b]	24.1%[b]	43.6%[c]	< 0.0001
Micrometastasis	3.6%[a]	6.2%[a]	12.1%[a]	12.7%[a]	
ITC	3.6%[a]	3.6%[a]	5.2%[a]	5.5%[a]	
Negative	83.7%[a]	70.7%[b]	58.6%[b]	38.2%[c]	

Fig. 6.6

[1] ML-χ^2 test for the overall trend differences among clinical stages.
[a-c] Marks of statistical significance of mutual differences among FIGO categories (ML-χ^2 test; $p < 0.05$): values marked by the same letter are not mutually significantly different.

FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumour cell; nSLN, non-SLN; SLN, sentinel lymph node.

REVISION QUESTIONS

1. What are the most significant prognostic factors in the early stages?
2. Can SLN biopsy improve surgical staging?
3. Is the presence of micrometastases (<2 mm) in LNs associated with a worse prognosis?

Principles of surgical treatment and postoperative morbidity

The principle of radical hysterectomy is the removal of tissue surrounding the cervix (parametrium) and the upper part of the vagina in addition to the uterus, with or without adnexa.

If the aim is to preserve fertility, the distal part of the cervix with the upper part of the vagina is removed with the parametrium (radical trachelectomy) or without it (simple trachelectomy).

If cervical cancer is diagnosed from the specimen after a simple hysterectomy, radical parametrectomy combined with upper vaginectomy can be performed with the aim of achieving the same outcome as the standard surgical procedure (radical hysterectomy).

Types of surgical procedure

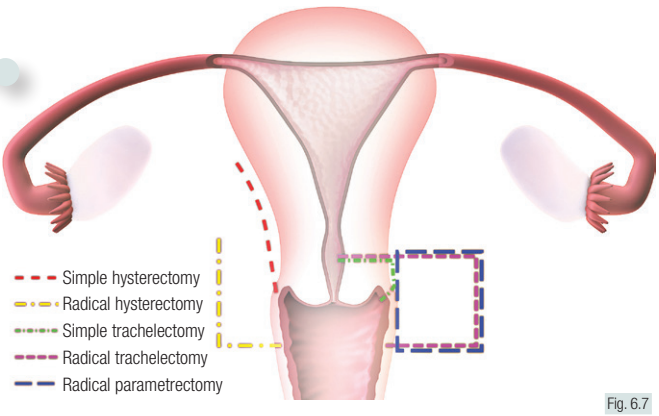
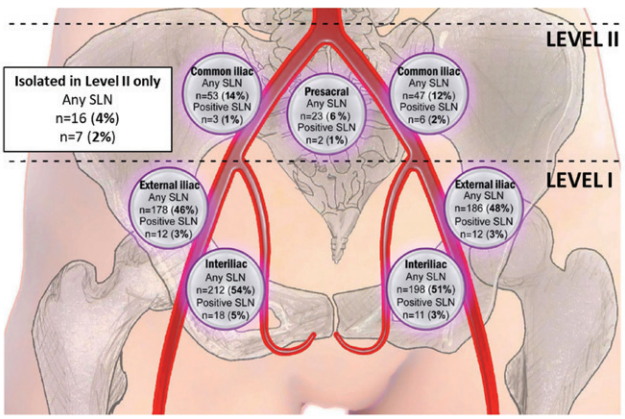


Fig. 6.7

Anatomical distribution of SLNs in the pelvis



SLN, sentinel lymph node.

Fig. 6.8

The standard procedure for surgical LN staging is a systematic pelvic lymphadenectomy (PLND), which should entail the removal of lymphatic tissue from the external, common and internal iliac regions bilaterally, and the presacral region.

SLNs are defined as the first LNs to which the primary cancer is likely to spread.

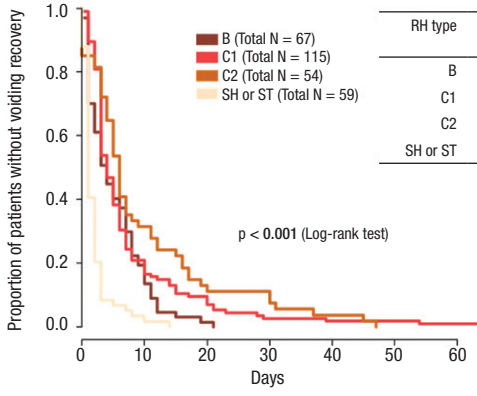
The majority of SLNs in CC are localised below the level of iliac bifurcation in the external and internal iliac regions.

Prevalence and severity of postoperative complications are mostly related to the radicality of parametrial resection.

The most prevalent are voiding dysfunctions such as incomplete bladder emptying and loss of bladder sensation; these present in 10%–50% of patients after radical hysterectomy.

Anorectal dysfunctions, mostly constipation and flatal incontinence, occur in 10%–30% of patients. Lymphoedema occurs in 20%–30% of patients and is a consequence of PLND.

Postoperative time to recovery from spontaneous voiding according to parametrial resection extent



RH type	Voiding recovery Mean days (SD)
B	5.2 (4.6)
C1	9.4 (28.5)
C2	9.8 (11.1)
SH or ST	2.0 (2.4)

Fig. 6.9

RH, radical hysterectomy; SD, standard deviation; SH, simple hysterectomy; ST, simple trachelectomy.

REVISION QUESTIONS

1. What is the principle of radical hysterectomy?
2. Which are the two pelvic regions where SLNs are most frequently located?
3. What is the most prevalent type of morbidity after radical hysterectomy?

Surgical treatment of early stages

Surgical LN staging is not indicated in stage IA1 LVSI-negative patients.

SLN biopsy (SLNB, without additional pelvic LN dissection) is an acceptable method of LN staging in stages IA1 LVSI-positive and IA2.

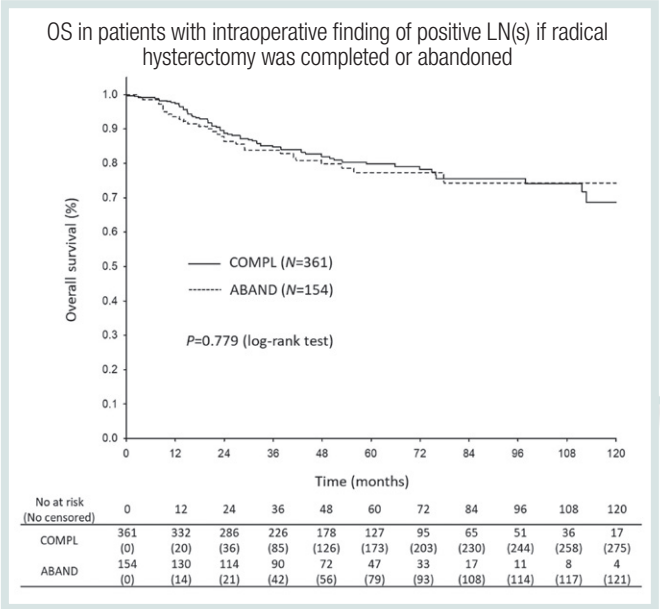
The standard LN staging procedure in patients with stage IB and IIA is systematic PLND.

Prevalence of LN metastatic involvement (N1) increases with disease stage

Stage	Number of cases	N1
IA1	505	0.3%
IA1 + LVSI	45	2.2%
IA2	421	3.1%
IB1	2709	13.8%
IB2	321	36.5%
IIA1	155	26.5%
IIA2	39	41.0%
IIB	148	46.6%

LN, lymph node; LVSI, lymphovascular space invasion.

Fig. 6.10



ABAND, cervical procedure abandoned intraoperatively; COMPL, cervical procedure completed as planned; LN, lymph node; OS, overall survival.

Fig. 6.11

SLNB should be routinely performed at the beginning of PLND.

Intraoperative assessment of (sentinel) LNs is recommended as the first step of surgical management.

If LN involvement is detected intraoperatively, further PLND and radical hysterectomy should be avoided. Patients should be referred for definitive chemoradiotherapy (CRT).

Simple hysterectomy or conisation is considered a sufficient procedure for stage IA CC due to a very low risk of parametrial involvement and an excellent prognosis.

Radical hysterectomy combined with pelvic LN staging is considered a standard surgical procedure for stages IB1/IB2/IIA1 CC.

Simple hysterectomy seems to be a safe alternative for patients with small tumours (≤2 cm) without deep stromal invasion according to the results of the SHAPE trial.

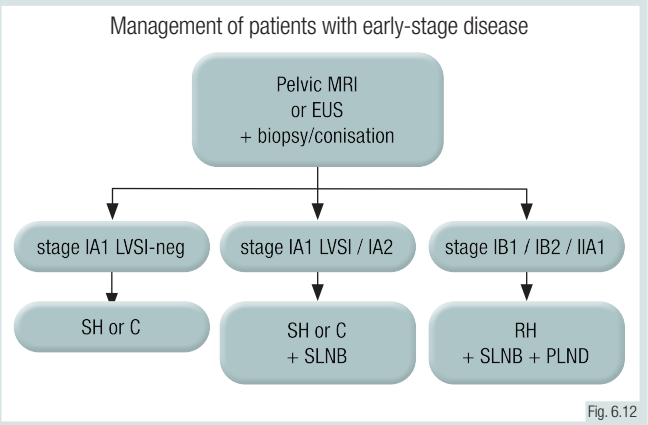


Fig. 6.12

C, conisation; EUS, expert ultrasound; LVSI, lymphovascular space invasion; MRI, magnetic resonance imaging; neg, negative; PLND, pelvic lymph node dissection; RH, radical hysterectomy; SH, simple hysterectomy; SLNB, sentinel lymph node biopsy.

REVISION QUESTIONS

1. What is the recommended LN surgical staging procedure in stage IA2?
2. What is the recommended management in patients originally scheduled for radical surgery if pelvic LN involvement is detected intraoperatively?
3. What is the standard surgical procedure in stage IB2?

Fertility-sparing treatment and the role of surgery in locally advanced or recurrent disease

The key selection criterion for fertility-sparing treatment in stage IB disease is a cranial extension of the tumour in the cervix, since its proximal part must be preserved for future pregnancy.

Additional selection criteria for fertility-sparing treatment candidates include tumour size (≤2 cm), histological type (squamous cell cancers or HPV-associated adenocarcinomas) and LN negativity.

Simple conisation, simple trachelectomy (partial cervix removal), radical vaginal or abdominal trachelectomy are the procedures of choice. Pregnancy outcome is directly related to the size of the remaining cervix, and less radical procedures seem to be safe in tumours <2 cm.

Key selection criterion for fertility-sparing surgery (isthmus–cranial tumour margin distance)

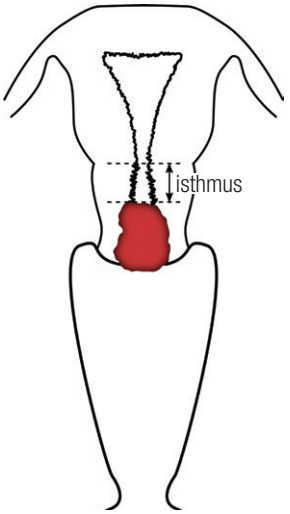


Fig. 6.13

Management of patients with locally advanced disease

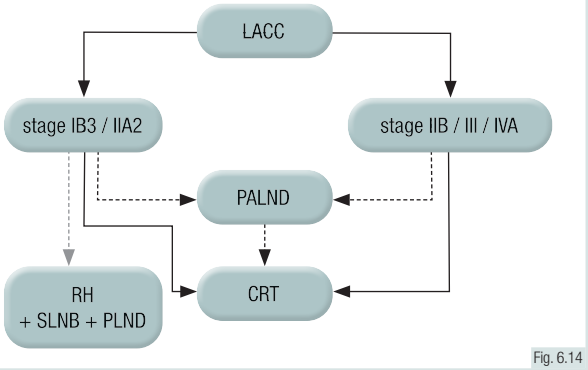


Fig. 6.14

CRT, chemoradiotherapy; LACC, locally advanced cervical cancer; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; RH, radical hysterectomy; SLNB, sentinel lymph node biopsy.

Radical surgery composed of radical hysterectomy and pelvic LN staging is an alternative treatment option to primary CRT in stages IB3/IIA2.

Para-aortic LN dissection (at least inframesenteric) may be considered in locally advanced CC with negative para-aortic LNs on imaging for staging purposes and for the planning of radiotherapy (RT).

Surgical debulking of positive pelvic LNs before CRT has not been proven to improve survival and therefore cannot be routinely recommended.

Pelvic exenteration (PE) is the treatment of choice in cases with central pelvic recurrence or tumour progression after primary pelvic RT in the absence of distant metastases.

PE can be performed as an anterior (preserving rectum), posterior (preserving urinary bladder and urethra) or total procedure, with consequent creation of a colostomy and/or urostomy.

In selected cases with recurrent tumours after primary RT with the attachment to the pelvic side wall, a laterally extended pelvic resection or even complex procedures including bone, nerve or large vessels should be considered as potentially curative options.

Side wall structures resectable during extended pelvic exenteration

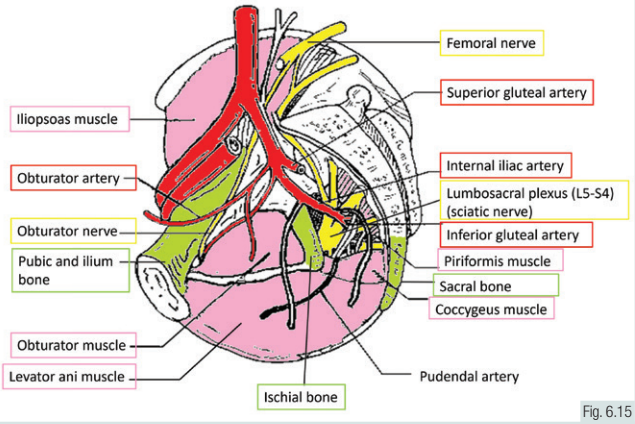


Fig. 6.15

Green: bones; pink: muscles; yellow: nerves; red: vessels.

REVISION QUESTIONS

1. What are the most important selection criteria for a fertility-sparing procedure?
2. Is a patient with distal (e.g. inguinal LN) recurrence a candidate for PE?
3. Is there a potentially curative option for patients with recurrent CC after primary RT if the tumour is attached to the pelvic side wall?

Summary: Staging and surgical treatment of cervical cancer

- Pretreatment staging: gynaecological examination (including colposcopy), biopsy, pelvic MRI or expert US
- Prognostic factors: LN involvement, tumour size, TFD, parametrial involvement, LVSI, stage and histological type
- The main principle of radical hysterectomy is removal of the parametrium and upper vagina together with the uterus
- Postoperative morbidity: (a) related to radical hysterectomy: voiding dysfunction, anorectal dysfunction; (b) related to lymphadenectomy: lymphoedema
- All LN metastases are associated with impaired prognosis; no clear cut-off size for better outcome has been identified
- Simple hysterectomy or conisation combined with SLNB is a standard treatment for stages IA1 LVSI-positive and IA2
- Radical hysterectomy combined with pelvic LN staging is a standard treatment for stages IB1/IB2/IIA1
- In large tumours (IB3, IIA2), radical hysterectomy combined with pelvic LN staging is an alternative treatment option to primary CRT
- Fertility-sparing treatments: the key selection criterion is cranial extension of the tumour in the cervix
- In cases with pelvic recurrence, PE or laterally extended endopelvic resection should be considered as potentially curative treatment options

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Image sources: **Fig. 6.5.** Cibula D, et al. Eur J Cancer 2021;158:111-122; **6.6.** Cibula D, et al. Gynecol Oncol 2012;124:496-501; **6.8.** adapted from Cibula D, et al. Eur J Cancer 2020;137:69-80; **6.9.** Zapardiel I, et al. Gynecol Oncol 2021;160:729-734; **6.10.** adapted from Cibula D, et al. Eur J Cancer 2021;158:111-122; **6.11.** Cibula D, et al. Eur J Cancer 2021;143:88-100; **6.15.** Cibula D, et al. Gynecol Oncol 2022;166:100-107. All other figures courtesy of the authors.

7 Non-surgical treatment of cervical cancer

Pre-therapeutic staging

For treatment decisions and definition of the radiation (nodal) volumes, information on lymph node (LN) involvement is mandatory.

Computed tomography (CT) and magnetic resonance imaging (MRI) have limited accuracy in primary LN staging.

^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET)–CT is the staging method of choice; however, false-negative rates of up to 20% have been reported. New tracers are under evaluation.

Detection of a pelvic LN in a 56-year-old woman with metastatic CC with FAPI-PET (A–C) and FDG-PET (D–F)

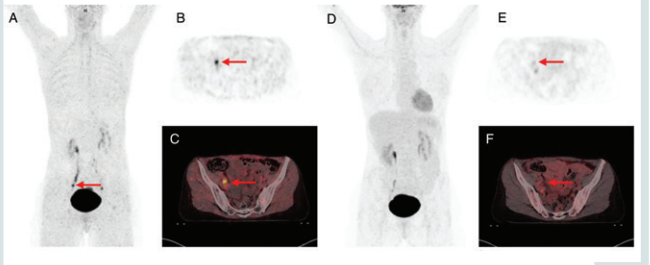


Fig. 7.1

CC, cervical cancer; FAPI, fibroblast activation protein inhibitor; FDG, fluorodeoxyglucose; LN, lymph node; PET, positron emission tomography.

DFS in patients with FIGO stage IIB CC favours laparoscopic staging with pelvic and PA lymphadenectomy

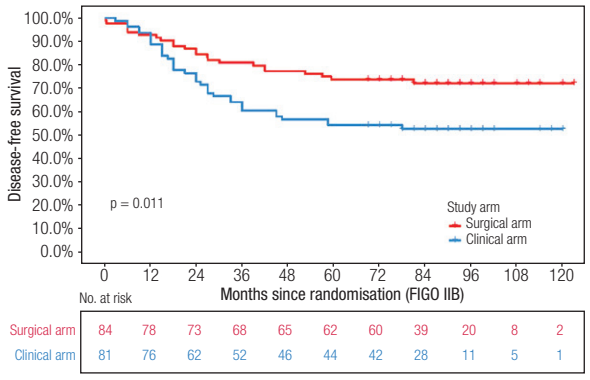


Fig. 7.2

CC, cervical cancer; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; PA, para-aortic.

Pretreatment laparoscopic staging (para-aortic [PA] nodes) provides histologically confirmed information on involved LN sites and has been explored in many centres.

A randomised phase III study (Uterus-11) demonstrated an additional survival benefit in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB cervical cancer (CC). One third of patients were upstaged.

Although surgical staging did not result in higher rates of treatment-related toxicity nor delay the start of chemoradiotherapy (CRT) in Uterus-11, other studies report poorer outcomes for patients who were surgically staged.

The Lymphadenectomy in Locally Advanced Cervical Cancer Study (LiLACS) combined the use of ^{18}F-FDG-PET scan and lymphadenectomy tailored after the results of the PET–CT scan.

The study planned to evaluate the potential benefit of lymphadenectomy in patients with CC and PET–CT-positive pelvic nodes, but negative PA nodes.

The study has been withdrawn, unfortunately.

LiLACS schema

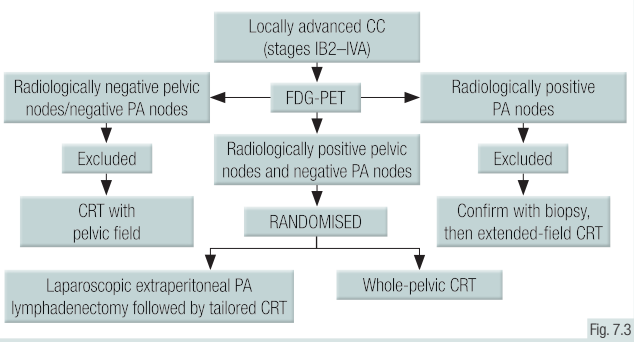


Fig. 7.3

CC, cervical cancer; CRT, chemoradiotherapy; FDG, fluorodeoxyglucose; LiLACS, Lymphadenectomy in Locally Advanced Cervical Cancer Study; PA, para-aortic; PET, positron emission tomography.

REVISION QUESTIONS

1. What are the limitations of CT and MRI in LN staging?
2. Which important benefit for the patient can be provided by surgical staging?
3. Does additional surgical staging delay primary treatment or increase morbidity?

Primary CRT

Primary CRT is the standard of care for all locally advanced (FIGO ≥IIB) and/or LN-positive CCs.

Patients with infiltration of the bladder and/or rectum can be treated either by CRT or primary anterior and/or posterior exenteration.

Both treatment modalities provide comparable oncological outcomes with different treatment-related morbidity (gastrointestinal toxicity and risk for fistulae versus loss of bladder and/or rectal function).

Locally advanced CC with infiltration of the urinary bladder

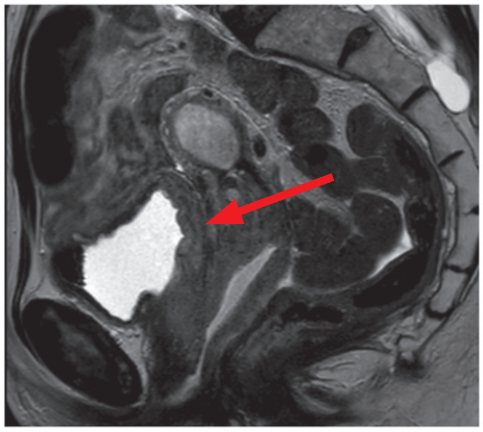
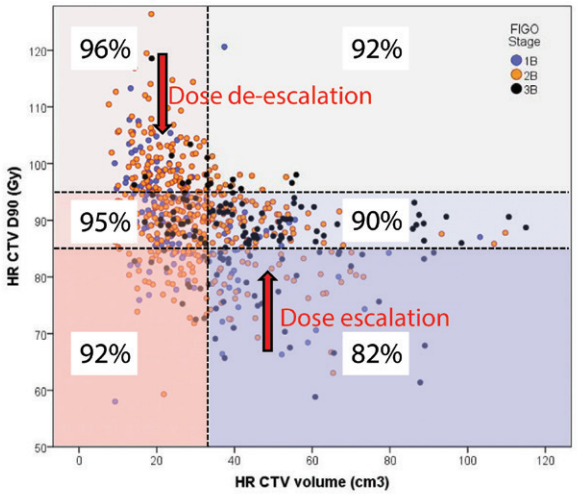


Fig. 7.4

CC, cervical cancer.

Dose–response relationship for primary CRT



Biologically equivalent doses of 85–90 Gy are needed to achieve sufficient local control.

Fig. 7.5

CRT, chemoradiotherapy; CTV, clinical target volume; D90 (Gy), dose of 90 Gy covering a volume (CTV_{HR}); FIGO, International Federation of Gynecology and Obstetrics; HR, high risk.

Primary CRT must combine external beam radiotherapy (EBRT) with chemotherapy (ChT) and intracervical brachytherapy. Because of tumour repair, total treatment duration should not be >8 weeks.

The biologically equivalent dose should be 85–90 Gy encompassing all visible tumour on MRI.

Omitting brachytherapy significantly compromises oncological outcome.

OS with and without brachytherapy for primary CRT

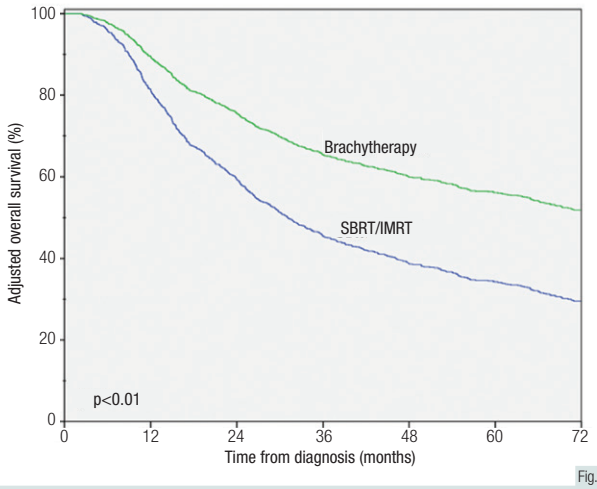


Fig. 7.6

CRT, chemoradiotherapy; IMRT, intensity-modulated radiotherapy; OS, overall survival; SBRT, stereotactic body radiotherapy.

Brachytherapy facilitates the delivery of high, biologically effective doses to the primary tumour and should not be replaced by other techniques.

Brachytherapy should be planned based on MRI and replanned according to tumour shrinkage (image-based adaptive treatment planning).

Although various dose concepts may be used for brachytherapy, the combination of brachytherapy and EBRT doses must result in a biologically effective dose of 85–90 Gy.

REVISION QUESTIONS

1. What is the standard of care for locally advanced CC?
2. Which parameters have an important impact on local control?
3. Why is a short total treatment time important for the outcome?

Radiotherapy (RT) techniques and radiosensitising

Adding weekly cisplatin to intensity-modulated RT (IMRT) improves local control and survival. There is no further benefit seen with 5-fluorouracil (5-FU)/ hydroxyurea (HU). Carboplatin can be substituted for patients with cisplatin intolerance.

The INTERLACE study explored weekly carboplatin and paclitaxel (×6) ChT prior to CRT. Initial results demonstrate improvements in disease-free survival (DFS). Final data are awaited.

Based on results from the OUTBACK trial, adjuvant ChT with carboplatin and paclitaxel is not indicated.

GOG-120: OS by treatment and number of patients at risk (for death) at 60 and 120 months

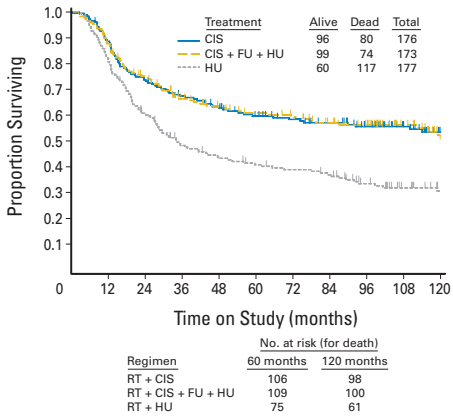


Fig. 7.7

CIS, cisplatin; FU, fluorouracil; HU, hydroxyurea; OS, overall survival; RT, radiotherapy.

Proton planning provides a reduced dose to normal tissues and reduces risk of secondary malignancies

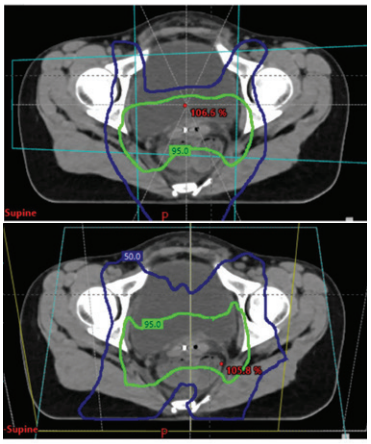


Fig. 7.8

Proton therapy (top) versus intensity-modulated radiotherapy (bottom).

IMRT techniques allow for 'dose-painting', encompassing the target volume for the prescribed dose, while reducing doses to organs at risk (bladder, small bowel, rectosigmoid, ovaries) and bone marrow.

Hyperthermia inhibits repair of RT/ChT damage and increases tumour cell kill. It may be an alternative for patients with locally advanced CC who are not fit enough for ChT.

Protons have a comparable biological effect to photons. The lower radiation doses to healthy normal tissues from proton beam therapy may reduce toxicity, especially RT-induced second malignancies.

CC is thought to be an immunogenic cancer. Additionally, CRT influences the microenvironment, causing immune stimulation/ inhibition. Not only does radiation induce neoantigens, but it activates pathways to augment response to immunotherapy, sometimes causing abscopal effects.

CALLA, a phase III, randomised, double blind, placebo-controlled multicentre study, demonstrated no significant oncological benefit for patients treated with CRT plus durvalumab versus CRT alone.

The KEYNOTE-A18 trial studied the combination of pembrolizumab with standard CRT followed by 3-weekly maintenance with pembrolizumab. Estimated overall survival (OS) at 24 months was 87%, with median OS not reached.

ENGOT-cx11/GOG-3047/KEYNOTE-A18: pembrolizumab+CRT vs placebo+CRT

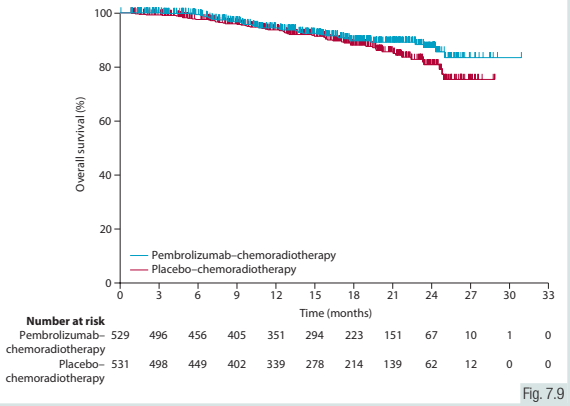


Fig. 7.9

CRT, chemoradiotherapy.

REVISION QUESTIONS

1. What are the benefits of IMRT techniques?
2. Why is simultaneous cisplatin ChT used for primary CRT?
3. How does RT interact with immunotherapy?

Fertility-sparing techniques (surgical)

Radiation causes permanent endometrial atrophy, preventing subsequent pregnancy.

Ovaries are extremely radiosensitive. The loss of ovarian function leads to premature menopause and has implications, e.g. increased risk of osteoporosis and cardiovascular diseases.

The transposition of the ovaries as far as possible from the radiation volume and the use of modern techniques allow for ovarian-sparing radiation.

Fixation of the ovaries with mobilised omentum and identification mark for planning CRT using titanium clips (orange)

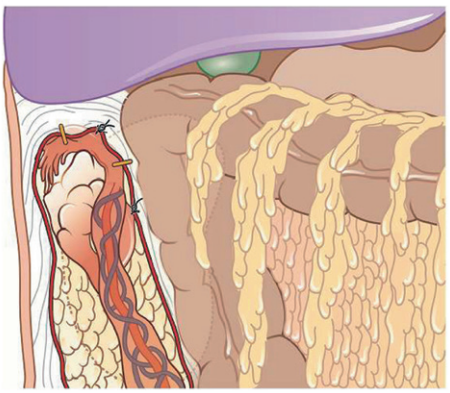
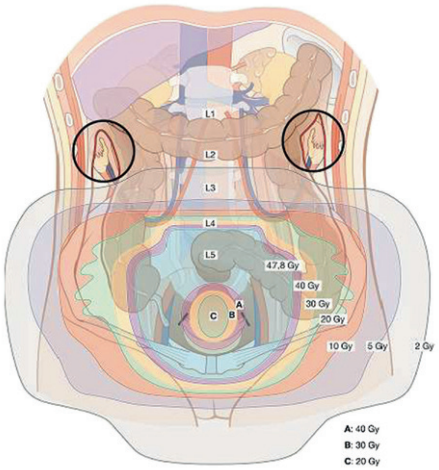


Fig. 7.10

CRT, chemoradiotherapy.

Anatomical distribution of radiation doses



Isodoses of the prescribed dose (47.8 Gy) in the target volume decreasing to the periphery and to the ovaries (in black circles) to <2 Gy between second (L2) and third (L3) lumbar vertebra. Selective dose reduction within the intact uterus from 40 Gy (A) to 30 Gy (B) in the periphery to 20 Gy (C) in the inner layer of the myometrium and endometrium.

Fig. 7.11

Ovarian transposition should reduce the dose to the ovaries to <2 Gy (mean).

Ovarian transposition is an oncologically safe option for patients <45 years of age with FIGO stage I–IIB CC.

Overall, the risk for ovarian metastases is low, but higher for adenocarcinomas compared with squamous cell carcinomas.

Uterine/ovarian transposition has been reported in patients with non-gynaecological malignancies prior to pelvic radiation for cancer.

Six patients resumed menstruation post treatment and two of three patients attempting to conceive post treatment were successful.

The most common surgical complication was cervical ischaemia causing necrosis and atrophy/stenosis. It is less likely to be successful in patients with CC.

Transparietal sutures are in place and ready to be tightened. Before that, the pneumoperitoneum was deflated

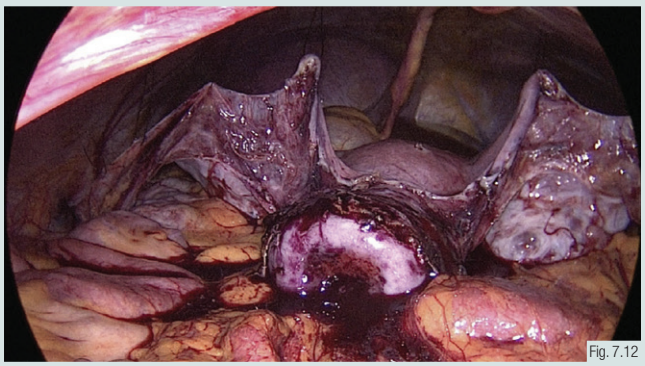


Fig. 7.12

REVISION QUESTIONS

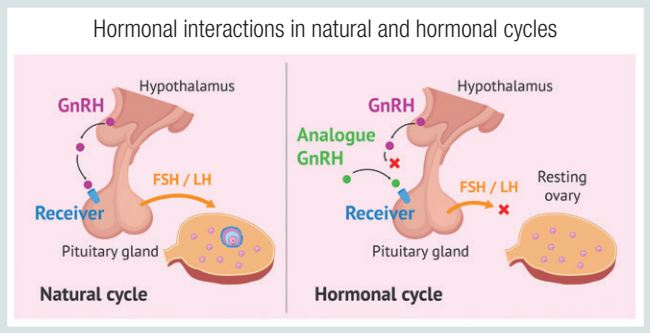
1. What are the reasons for radiation-induced infertility?
2. Which parameter is the most important when performing ovarian transposition?
3. What is the dose recommendation for ovarian sparing?

Fertility-sparing techniques (pharmacological)

In addition to surgical techniques, there are pharmacological options for protecting ovarian function from ChT.

ChT-induced ovarian toxicity may be reduced by depriving the ovaries of cycling hormones inhibiting rapid cellular turnover on growing follicles.

This effect may be transiently achieved by using gonadotropin-releasing hormone (GnRH) agonists or oral contraceptives.



FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH luteinising hormone.

Fig. 7.13

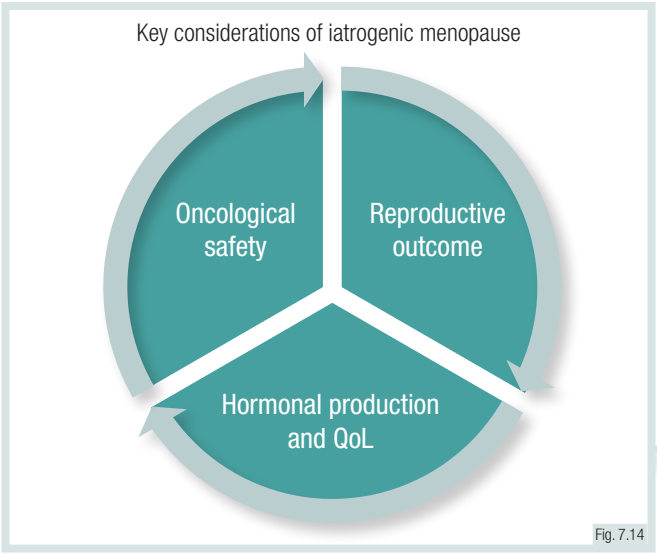


Fig. 7.14

QoL, quality of life.

There is evidence in animals that GnRH agonists reduce the risk of ChT-induced ovarian damage.

There is reasonable evidence that this strategy doubles the chance for resumption of menses from 45% to 90% in patients with breast or haematological cancers. Spontaneous pregnancy rates following cancer treatment with GnRH protection are also twice as good (~40% versus 20%).

GnRH agonists may be, in some studies, beneficial for protection of menstrual function, but there is no evidence that they improve the rate of spontaneous pregnancy after ChT.

Ovarian follicles are still exposed to the toxic DNA-damaging agents, despite the GnRH analogue-induced suppression of the ovarian hormone production.

Resumption of menstruation remains a poor predictor of fertility, since women who menstruate can remain infertile after toxic ChT.

Studies that measured anti-Müllerian hormone (AMH) and antral follicle count have not reported any benefit of GnRH agonists to resume menstruation.

Fig. 7.15

REVISION QUESTIONS

1. What pharmacological options are available for younger women to protect ovarian function?
2. How efficient is chemoprotection for resumption of menstruation and likelihood of spontaneous pregnancy?
3. Can GnRH analogues be routinely administered in young women undergoing ChT?

Summary: Non-surgical treatment of cervical cancer

- Primary CRT is the standard of care for all locally advanced and/or LN-positive CC
- Surgical staging prior to CRT is not part of routine practice. No good evidence exists for this strategy in patients with CC, where surgical options are preferable
- IMRT techniques allow the optimisation of dose to target, while reducing the risks to adjacent organs/healthy tissue
- Brachytherapy is an essential part of the RT treatment and should not be omitted or replaced
- Exenterative surgery is an option in patients with locally advanced disease involving the bladder/rectal mucosa (stage IVA)
- Adjuvant ChT cannot be recommended after the results of the OUTBACK trial
- Novel immunotherapeutic approaches are now emerging in the treatment of CC
- Current and future studies will evaluate the role of adjuvant, concomitant and simultaneous immunotherapy in combination with primary CRT
- Surgical approaches of ovarian and/or uterine transposition are options to preserve fertility

Further Reading

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Image sources: **Fig. 7.1.** Wegen S, et al. Clin Nucl Med 2023;48:150-155; **7.2.** Marnitz S, et al. Int J Gynecol Cancer 2020;30:1855-1861; **7.3.** Frumovitz M, et al. J Minim Invasive Gynecol 2014;21:3-8; **7.4.** courtesy Prof. C. Köhler; **7.5.** Pötter R, et al. Clin Transl Radiat Oncol 2018;9:48-60; **7.6.** Gill BS, et al. Int J Radiat Oncol Biol Phys 2014;90:1083-1090; **7.7.** Rose PG, et al. J Clin Oncol 2007;25:2804-2810; **7.8.** Taunk N. Int J Gynecol Cancer 2022;32:414-420; **7.9.** Lorusso D, et al. Lancet 2024;103:1341-1350; **7.10, 7.11** Ghadjar P, et al. Radiat Oncol 2015;10:50; **7.12.** Ribeiro R, et al. Fertil Steril 2017;108:320-324.e1; **7.13.** https://www.invitra.com/en/gnrh-analogues/; **7.14, 7.15.** courtesy of the authors.

B

More advanced knowledge

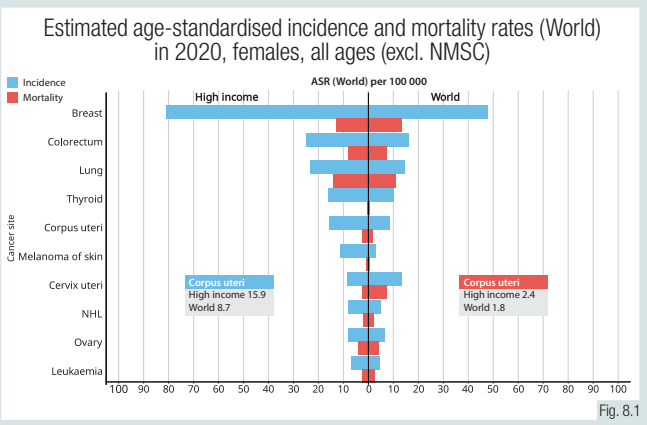
8 Epidemiology and risk factors for ovarian, uterine and cervical cancers

Epidemiology and risk factors for uterine cancer

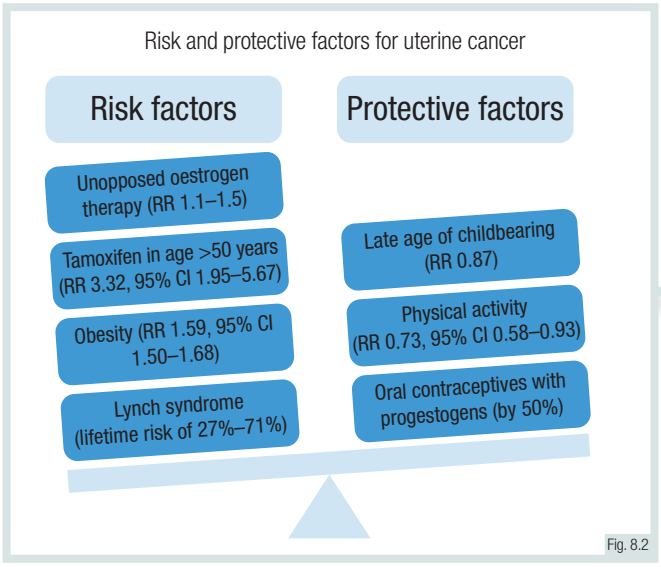
Uterine carcinoma (UC) is the most common gynaecological cancer in developed countries and the second most frequent, after cervical cancer, in developing countries.

The incidence of UC is rising due to the increasing global prevalence of excess body fat (overweight, and especially obesity) and ageing.

Median age at diagnosis is 62 years, but 2%–5% of UCs occur in women <40 years old. At diagnosis, nearly 68% of cases are limited to the uterus.



ASR, age-standardised rate; NHL, Non-Hodgkin lymphoma; NMSC, non-melanoma skin cancer.



CI, confidence interval; RR, risk ratio.

Risk factors:

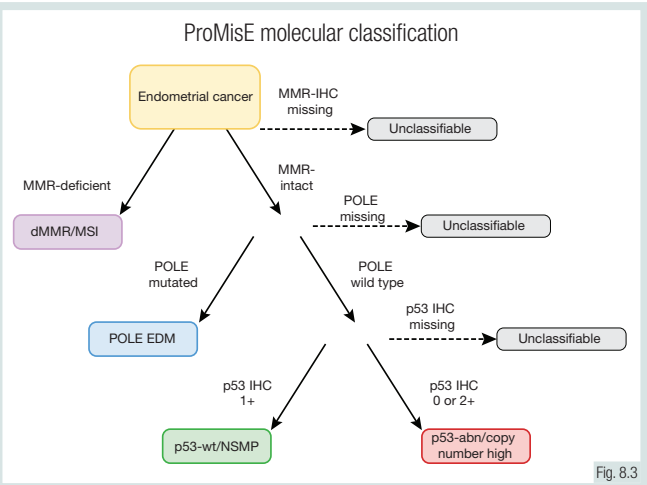
- Endogenous oestrogens found in obesity, chronic anovulation (e.g. polycystic ovary syndrome), oestrogen-secreting tumours, early menarche and late menopause.
- Exogenous unopposed oestrogen therapy or selective oestrogen receptor modulators (e.g. tamoxifen).

Protective factors: Progestogens, childbearing (especially at an older age, >40 years old), physical activity, coffee and green tea.

The Cancer Genome Atlas (TCGA) established four molecular subtypes of UC, simplified by the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE): polymerase epsilon (*POLE*) ultramutated (*POLE*mut), microsatellite instability/mismatch repair-deficient (MSI/dMMR), p53 abnormal (p53-abn) and no specific molecular profile (NSMP).

These subtypes have different prognoses, with the best outcome for the *POLE*mut subgroup, followed by MSI/dMMR and NSMP, the worst outcome being for the p53-abn subtype.

Immunohistochemistry (IHC) may be used for molecular classification, but further genomic testing is required to determine hereditary implications.



abn, abnormal; dMMR, mismatch repair-deficient; EDM, exonuclease domain mutation; IHC, immunohistochemistry; MSI, microsatellite instability; MMR, mismatch repair; NSMP, no specific molecular profile; p53-abn, p53-abnormal; p53-wt, p53-wild type; POLE, polymerase epsilon; ProMisE, Proactive Molecular Risk Classifier for Endometrial Cancer.

REVISION QUESTIONS

1. Which is the most common gynaecological cancer in developing countries?
2. Is polycystic ovary syndrome considered as a risk or a protective factor for UC?
3. Which molecular subtype of UC is associated with the best outcome?

Epidemiology and risk factors for ovarian cancer

Ovarian cancer (OC) is the second most common gynaecological cancer in developed countries and represents the leading cause of gynaecological cancer death.

90% of OCs are epithelial, and 75% of these are high-grade serous carcinomas (HGSCs). Median age at diagnosis is 63 years.

70%-80% of patients with epithelial OC are diagnosed at an advanced stage (III/IV).

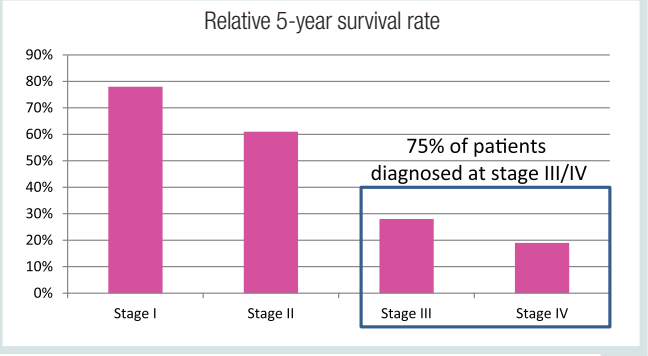


Fig. 8.4

Risk factors for ovarian cancer

INCESSANT OVULATION		BENIGN CONDITIONS		HEREDITARY SYNDROMES	
Menopause >52y	Parous vs nulliparous	Endometriosis for specific subtypes	Polycystic ovarian syndrome	*BRCA* syndrome	Lynch syndrome
RR 1.46 (95% CI 1.06–1.99)*	RR 0.71 (95% CI 0.59–0.87)*	• Clear cell (OR 3.05, 95% CI 2.43–3.84) • Endometrioid (OR 2.04, 95% CI 1.67–2.48) • Low-grade serous (OR 2.11, 95% CI 1.39–3.20)	OR 2.52 (95% CI 1.08–5.89)	• 15% of cases • Median age 50y • Lifetime risk for *BRCA1*: 35%–45%, for *BRCA2*: 15%–25% • Better prognosis	• 1% of cases • Lifetime risk 3%–14%

*European Prospective Investigation into Cancer and Nutrition (EPIC) has followed over 300 000 women with 878 cases of epithelial OC.

Fig. 8.5

CI, confidence interval; OC, ovarian cancer; OR, odds ratio; RR, risk ratio.

OC risk increases with age, and is associated with a higher number of ovulatory cycles (e.g. early menarche, late menopause, nulliparity and infertility).

Endometriosis is associated with endometrioid, clear cell and low-grade serous OC subtypes. The risk of malignant transformation is up to 2.5%.

An inherited predisposition for OC is found in those carrying mutations in DNA repair genes such as *BRCA* (in ~15% of OCs), mismatch repair (1%, Lynch syndrome), *BRIP1* and *RAD51C/D*.

Other proposed risk factors include family history of non-*BRCA* breast cancer, obesity, polycystic ovary syndrome and hormone replacement therapy (HRT), although none are clearly proven.

Factors protecting against OC include: oral contraceptives, tubal ligation, bilateral salpingo-oophorectomy, hysterectomy, parity and breastfeeding.

Protective factors for ovarian cancer

Oral contraceptives	• Any use reduces risk with RR 0.73 (95% CI 0.70–0.76) • Protective effect increases with longer duration and persists after cessation
Tubal ligation	• Nurses' Health Study showed a risk reduction (HR 0.76; 95% CI 0.64–0.90) more significant for non-serous (RR 0.57; 95% CI 0.40–0.82) • A meta-analysis demonstrated a great benefit in non-serous OC
Hysterectomy without oophorectomy	• Demonstrated the risk reduction of OC in a meta-analysis (OR 0.66; 95% CI 0.50–0.86) and in the Nurses' Health Study (OR 0.80; 95% CI 0.66–0.97)
Salpingo-oophorectomy	• Reduces the risk of developing OC by 95% but there is a 1%–4% risk of primary peritoneal cancer
Breastfeeding	• A meta-analysis showed a 30% reduced risk of OC when comparing women who had breastfed and those who had not (pooled RR 0.70; 95% CI 0.64–0.76) • Protective effect is duration-dependent

Fig. 8.6

CI, confidence interval; HR, hazard ratio; OC, ovarian cancer; OR, odds ratio; RR, risk ratio.

REVISION QUESTIONS

1. What is the most common histological subtype and stage at presentation of OC?
2. List some important risk factors for developing OC.
3. Which factors protect women from developing OC?

Epidemiology and risk factors for cervical cancer

Cervical cancer (CC) is the fourth most common female cancer, worldwide. In the developing world, it is both the second most frequent cancer and second highest cause of cancer-related deaths in women.

87% of new CC cases occur in developing countries. It is the most diagnosed cancer in women in 23 countries (out of 185) and the leading cause of death in 36.

Screening programmes have reduced the incidence of invasive CC by 60%–80%. In developed countries, the median age at diagnosis is 53 years.

Top cancer per country, estimated number of deaths in 2020, females, all ages (excl. NMSC)

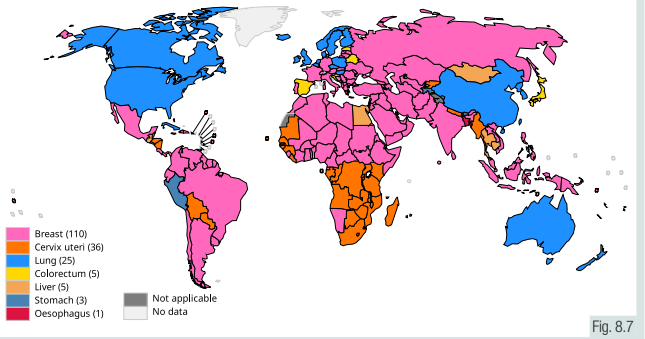
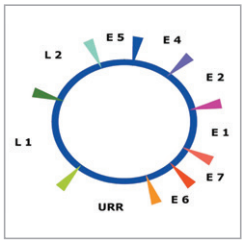


Fig. 8.7

NMSC, non-melanoma skin cancer.

Aetiology and risk factors for cervical cancer

HPV genome



RISK FACTORS:

- Early onset of sexual activity (twofold for <18 years of age)
- Multiple sexual partners (threefold for ≥6 partners)
- A high-risk sexual partner (i.e. multiple previous partners)
- History of sexually-transmitted infections (herpes, Chlamydia)
- History of vulvar or vaginal intraepithelial neoplasia or cancer
- Immunosuppression (HIV)
- Oral contraceptives
- Smoking (for squamous histology)

Fig. 8.8

HPV, human papillomavirus; HIV, human immunodeficiency virus; URR, upstream regulatory region.

Human papillomavirus (HPV) causes 99.7% of CC cases. HPV types 16 and 18 are responsible for 70% of all cases.

Histologically, approximately 69% are squamous cell carcinomas and 25% are adenocarcinomas. Although 70%–80% of sexually active adults acquire HPV, only a minority of women <50 years of age develop CC.

The risk factors for developing CC are usually related to a reduced immune response to HPV or an increased risk of acquiring this virus.

Screening has reduced CC incidence and mortality. Methods include Papanicolaou test (cytology), HPV testing (DNA detection of oncogenic types of HPV) or both.

In a meta-analysis of 12 case-control studies, cytology screening was associated with decreased risk of invasive CC (odds ratio 0.35, 95% confidence interval [CI] 0.30–0.41).

HPV testing is more sensitive than cytology. This increases referrals for colposcopy and earlier diagnosis, but may not alter overall survival in the long term. HPV vaccination is available from prepuberty to 45 years old for both sexes.

Comparison of cervical cancer screening guidelines

	ACS (2020)	USPSTF (2018)	WHO (2021)	ESGO/EFC (2020)
Age to initiate	<25y no screening	Cervical cytology alone every 3y from 21 to 29y	<25-30y no screening	<25y no screening
Recommended screening test & frequency	Age ≥25y primary HPV test alone every 5y, co-testing every 5y or cytology alone every 3y	Screening every 3y with cytology alone, every 5 years with high-risk HPV testing alone, or every 5y with co-testing	Primary HPV test every 5-10y or cytology every 3y, starting at the age of 30y or at the age 25y if HIV+	Primary HPV test every 5y starting at least at age 30y
Age to discontinue	>65y discontinue screening if adequate negative prior screening. If not, continue screening until criteria for cessation are met	>65y no screening in women with adequate prior screening and who are not otherwise at high-risk cervical cancer	>50y, stop screening after 2 consecutive negative screening results	Testing recommended until the age of 65y. Those with negative screening test at age 65 can exit the programme
After hysterectomy	No screening if removal of cervix and no prior high-grade pre-cancer or cervical cancer	No screening if hysterectomy and no prior high-grade pre-cancer or cervical cancer	Not indicated	Not indicated
HPV vaccinated	Follow age-specific screening recommendations (as unvaccinated individuals)	Continue age-specific screening recommendations, until further evidence accrues	Not indicated	Continue age-specific screening recommendations

Fig. 8.9

ACS, American Cancer Society; ESGO/EFC, European Society of Gynaecological Oncology/European Federation for Colposcopy; HIV, human immunodeficiency virus; HPV, human papillomavirus; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

REVISION QUESTIONS

1. Is CC incidence the same across different regions of the world?
2. Are all the risk factors for developing CC associated with HPV transmission?
3. Is there a unique screening programme for CC?

Summary: Epidemiology and risk factors for ovarian, uterine and cervical cancers

- UC is the most common gynaecological cancer in developed countries
- The main risk factor for endometrioid UC is long-term endogenous or exogenous exposure to oestrogens
- Lynch syndrome carriers have a lifetime risk of UC of 27%–71% and this accounts for 2%–5% of UC cases. Most will present at younger ages (46–54 years)
- The newly established molecular UC classification (ProMisE) includes four subtypes: *POLE*mut, MSI/dMMR, NSMP and p53-abn
- OC is the second most common gynaecological cancer in developed countries, but the most common cause of gynaecological cancer death. It is the fifth leading cause of cancer death in women
- Approximately 15% of patients with high-grade serous/endometrioid OCs have germline *BRCA* mutations
- Endometriosis is associated with non-serous OC. Oral contraceptives, tubal ligation, bilateral salpingo-oophorectomy, hysterectomy and breastfeeding are protective factors for OC
- CC is the second leading cause of cancer-related deaths in women in developing countries
- HPV is implicated in 99.7% of CC cases. Risk factors for acquiring HPV and a decrease in immunity lead to an increased risk of CC
- CC screening and HPV vaccination are the most effective strategies in CC prevention

Further Reading

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9 Diagnosis and treatment of vulvar cancer

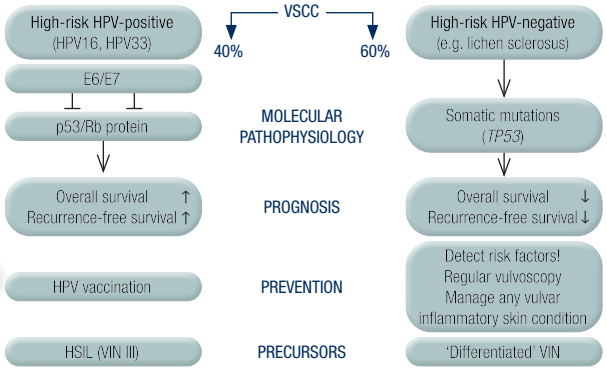
Pathology and molecular biology

Vulvar squamous cell carcinoma (VSCC) represents 90% of epithelial malignant vulvar tumours.

Incidence has been rising since 1990, although overall VSCC is a rare disease accounting for only 4% of all gynaecological malignancies, worldwide.

The majority of VSCCs still arise independent of human papillomavirus (HPV) infection and are linked to chronic inflammatory skin diseases such as lichen sclerosus, triggered by *TP53* mutations. Approximately 40% of VSCCs are related to high-risk HPV, with HPV16 being the most identified subtype.

Schematic overview of the molecular pathophysiology in vulvar carcinoma



HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; Rb, retinoblastoma; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma. Fig. 9.1

Immunohistochemistry examples: p16 and p53

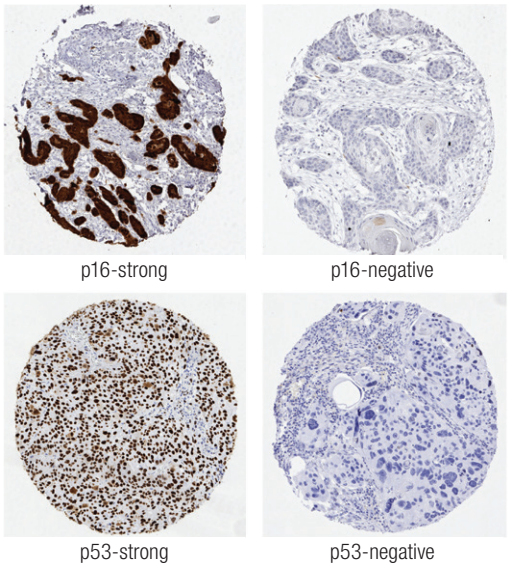


Fig. 9.2

p16 overexpression, detected with immunohistochemistry (IHC), is a known surrogate marker for HPV-associated transformation, whereas aberrant p53 expression is linked to HPV-independent VSCC.

Precursor lesions of VSCC are divided into HPV-dependent high-grade squamous intraepithelial lesion (HSIL; high-grade vulvar intraepithelial neoplasia [VIN]) and HPV-independent 'differentiated' VIN (dVIN), which has a higher progression rate to invasive cancer.

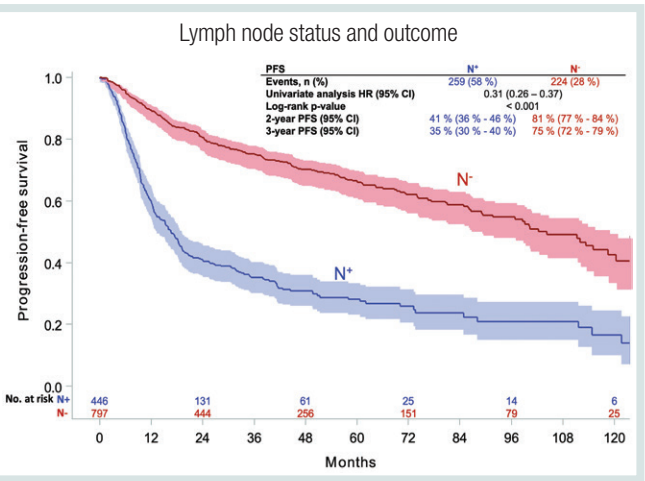
It is estimated that prophylactic HPV vaccination can prevent one third of VSCCs. Regular vulvoscopy in case of chronic skin disease can detect dVIN early, and therefore help prevent progression to HPV-negative VSCC.

p16 overexpression is associated with an improved prognosis, while mutant p53 expression presages poorer outcomes.

Inguinofemoral lymph nodes (LNs) are the first sites of metastatic spread and an important prognostic marker in VSCC. Distant metastases are rare and occur late.

Three-year progression-free survival (PFS)/overall survival (OS) rates for node-positive (N+) patients are 35.2% and 56.2%, respectively, compared with 75.2% and 90.2% for node-negative (N-) patients.

Lymph node status and outcome



CI, confidence interval; HR, hazard ratio; N+, node-positive; N-, node-negative; PFS, progression-free survival. Fig. 9.3

REVISION QUESTIONS

1. What percentage of VSCCs arise independent of HPV infection?
2. Which HPV subtype is the most predominant in HPV-associated VSCC?
3. What is the first site of metastatic spread in VSCC?

Clinical presentation, symptoms and diagnosis

Itching, burning and soreness can be early symptoms of VIN and/or VSCC. However, VSCC can also be asymptomatic.

In clinical presentation, early lesions may appear as warty, erosions/ulcers, hyperkeratotic or red lesions.

Foul-smelling discharge, pain, swelling of the groins with subsequent lymphoedema can occur as late symptoms.

Clinical presentation of (a) HSIL (VIN III); (b) dVIN; (c) VSCC

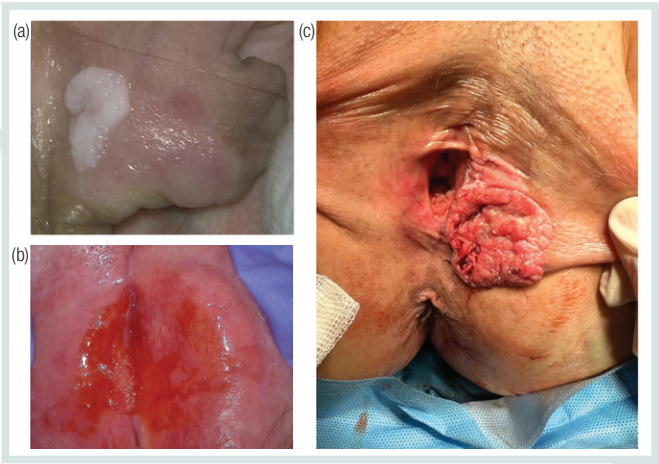


Fig. 9.4

dVIN, differentiated VIN; HSIL, high-grade squamous intraepithelial lesion; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma.

TNM classification of vulvar cancers, 8th edition

TNM categories (8th edition)	Definition
Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1a	Lesions ≤2 cm in size, confined to the vulva/perineum with stromal invasion ≤1.0 mm
T1b	Lesions >2 cm in size, confined to the vulva/perineum with stromal invasion >1.0 mm
T2	Tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus)
T3	Tumour invades upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	*One or two regional lymph nodes with the following features:*
N1a	One or two node metastasis(es), each <5 mm
N1b	One lymph node metastasis ≥5 mm
N2	*Regional lymph node metastasis with the following features:*
N2a	Three or more lymph node metastases, each <5 mm
N2b	Two or more lymph node metastases ≥5 mm
N2c	Lymph node metastasis with extracapsular spread
N3	Fixed or ulcerated regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

TNM, Tumour, Node, Metastasis.

Fig. 9.5

Thorough clinical examination including the complete anogenital region aims to determine multifocality, multicentricity, tumour size and possible infiltration of the urethra, vagina, anal region and/or bones.

Histopathological diagnosis is usually made via (punch) biopsy to determine the invasion depth of the tumour. Multifocal lesions require multiple biopsies.

Clinical examination should include palpation and ultrasound of the groins to evaluate regional LNs. Cross-sectional imaging and/or nodal biopsy can be performed to gain further information on nodal involvement and local tumour growth.

Ultrasound of a suspicious lymph node of the groin

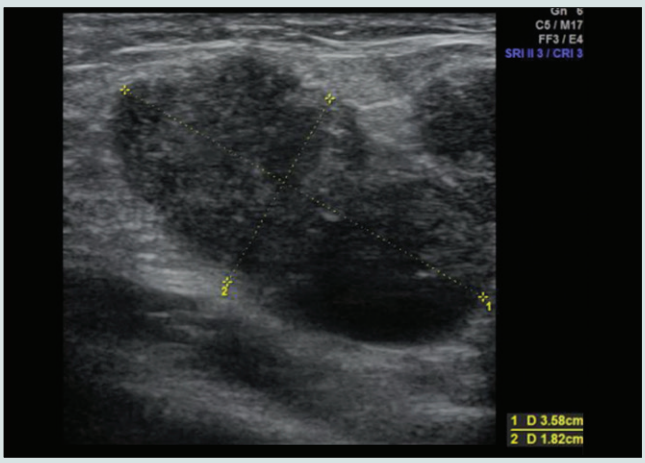


Fig. 9.6

Patients with vulvar cancer should be monitored closely during the first 3 years (at least every 3 months) for recurrent disease with gynaecological examination, ultrasound (groin) and vulvoscopy.

HPV vaccination can reduce risk of recurrence in 'usual type' VIN and HPV-associated VSCC.

Underlying skin disease (e.g. lichen sclerosus) should be treated with highly potent topical steroids to prevent/minimise risk of further malignancy.

REVISION QUESTIONS

1. Describe the early symptoms of VIN and VSCC.
2. Can HPV vaccination prevent vulvar cancer?
3. How should physicians monitor patients for recurrent disease?

Treatment

Radical wide local excision is recommended whenever possible, with primary reconstructive plastic surgery of the vulva, if necessary.

Tumour-free surgical margins of 1 cm are recommended for local control, where possible. However, less clearance is acceptable adjacent to critical structures such as urethra/clitoris.

Precancerous lesions, especially 'usual type' VIN, can be treated with laser excision/vaporisation.

Radical wide excision of the vulva with primary reconstructive plastic surgery

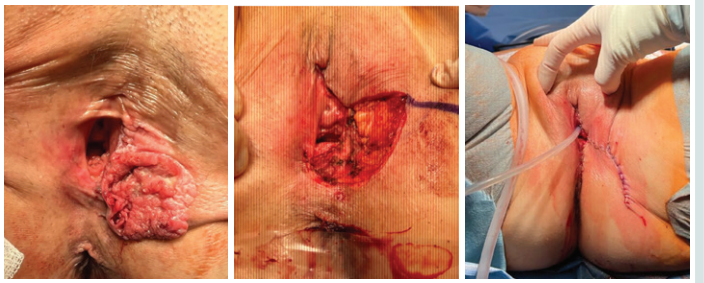
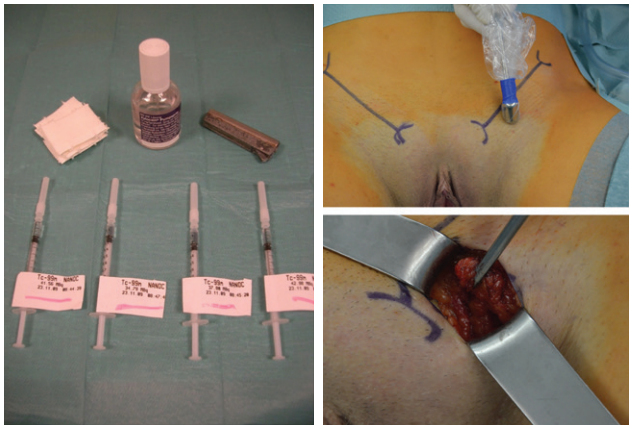


Fig. 9.7

SLN mapping of the groins



SLN, sentinel lymph node.

Fig. 9.8

If the VSCC is a unifocal tumour, <4 cm diameter and there are no suspicious inguinal nodes on cross-sectional imaging or ultrasound (GROINSS-V criteria), sentinel lymph node biopsy (SLNB) is recommended.

Detection of involved (sentinel) nodes with a gamma detector is performed after injection of technetium radioisotope into the tumour surroundings. SLNB reduces the risks of lymphoedema, lymphocoele and infection.

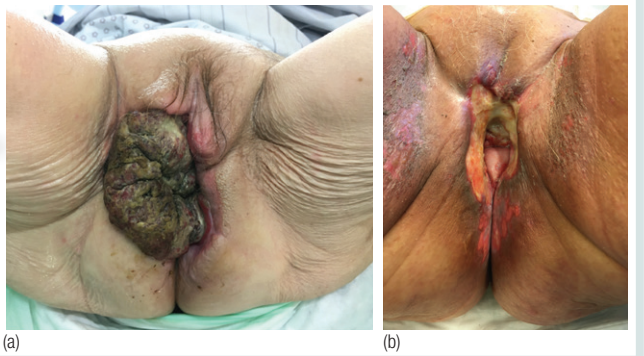
Patients with obvious inguinal node involvement require lymphadenectomy on the affected side for therapeutic purposes.

In comparison with other tumour types, molecular pathological information does not affect clinical treatment decisions in patients with VSCC, at the time of publication.

Adjuvant radio(chemo)therapy is additionally applied in high-risk disease.

In advanced/metastatic vulvar cancer, systemic treatment should be individualised and is mostly experimental and adapted from other HPV-induced cancers, such as anal or cervical cancer.

Examples of locally advanced VSCC: (a) planned for primary chemoradiotherapy and (b) after chemoradiotherapy, with pathological complete remission



(a) (b)

VSCC, vulvar squamous cell carcinoma.

Fig. 9.9

REVISION QUESTIONS

1. When is SLNB indicated?
2. What are common side effects of inguinal lymphadenectomy?
3. What is used for sentinel LN mapping?

Summary: Diagnosis and treatment of vulvar cancer

- VSCC is a rare malignancy of the female genital tract
- HPV vaccination can prevent one third of VSCCs
- dVIN is rare (~5% of VIN cases) but has a high risk of malignant transformation and is the precursor of HPV-independent VSCC; 'usual type' VIN is the precursor of HPV-dependent VSCC
- Radical local excision with primary reconstructive plastic surgery and SLNB is the treatment of choice in early-stage VSCC
- SLNB is indicated only if the 'GROINSS-V criteria' apply: unifocal primary tumour, <4 cm diameter, negative inguinal nodes on clinical exam and ultrasound
- Inguinal lymphadenectomy is required for patients with positive LNs
- Surgeons should aim for tumour-free surgical margins of 1 cm; a less radical approach is accepted to preserve critical structures

Further Reading

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10 Rare gynaecological cancers

Epidemiology, initial management and networking

Rare cancers (i.e. those with an incidence of <6/100 000 persons/year) collectively represent >20% of all cancers diagnosed worldwide.

More than 50% of all gynaecological neoplasms are rare tumours. Based on RARECARE consortium data, ~87 000 cases are diagnosed annually in the European Union.

Rarity may be due to tissue of origin, specific histological subtype or localisation. Classification relies on distinct histological and molecular features.

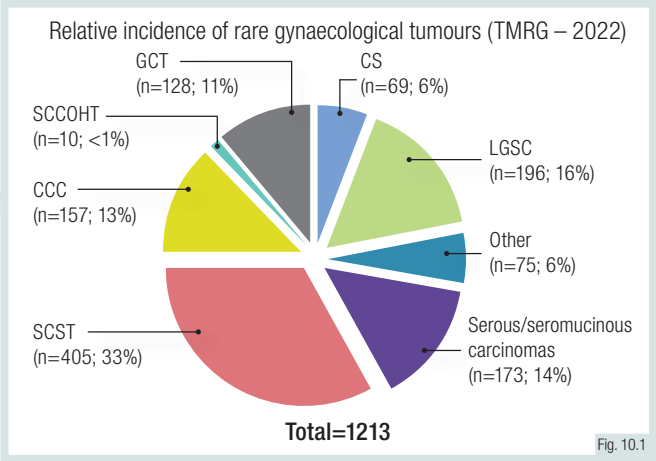


Fig. 10.1

CCC, clear cell carcinoma; CS, carcinosarcoma; GCT, germ cell tumour; LGSC, low-grade serous carcinoma; SCCOHT, small cell carcinoma of the ovary, hypercalcaemic type; SCST, sex cord-stromal tumour; TMRG, Tumeurs Malignes Rares Gynécologiques.

Global management of rare gynaecological tumours

Diagnostic process
- Referral to expert centre
- Expert pathological review
- Molecular biology characterisation

Treatment considerations
- Optimal quality surgery?
- Adjuvant treatment?
- Fertility?

Fig. 10.2

Histological review by an expert pathologist is the cornerstone of accurate diagnosis and appropriate management, as discordance has been reported in 10%-35% of rare gynaecological tumours.

Initial treatment relies on surgery with quality criteria, such as rigorous examination of the peritoneal cavity and multiple biopsies; suboptimal surgery may lead to re-operation.

Adjuvant systemic treatment and follow-up mainly depend on histological subtype and International Federation of Gynecology and Obstetrics (FIGO) stage. Compromised fertility is a major concern for younger patients.

Until 2010, the vast majority of rare gynaecological tumours were treated as a global entity, despite distinct pathological patterns; more recently, harmonisation of specific treatments has emerged.

Several national dedicated expert networks, such as TMRG (Tumeurs Malignes Rares Gynécologiques) in France and RaNGO (Rare Neoplasms of Gynaecological Origin) in the UK, provide a platform for clinicians: from daily support to clinical trials development and participation.

Supranational consortia (e.g. EURACAN [European Reference Network for Rare Adult Solid Cancers], ENGOT [European Network of Gynaecological Oncological Trial groups]) and global collaborations (GCIG [Gynecologic Cancer InterGroup]) are of prime importance, notably for data sharing and development of dedicated clinical trials.

Strong networking for rare tumours

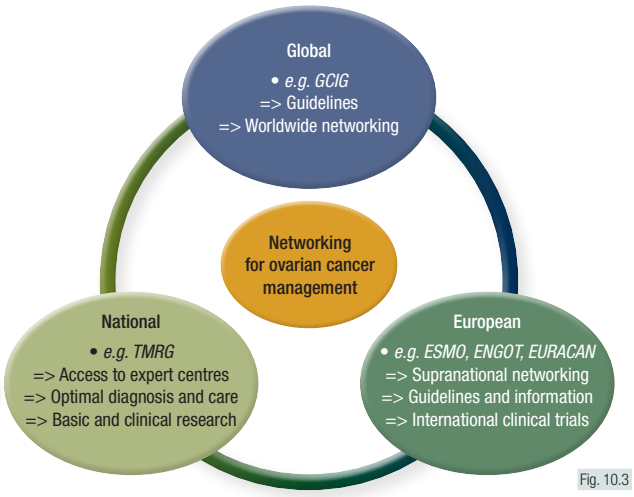


Fig. 10.3

ENGOT, European Network of Gynaecological Oncological Trial groups; ESMO, European Society for Medical Oncology; EURACAN, European Reference Network for Rare Adult Solid Cancers; GCIG, Gynecologic Cancer InterGroup; TMRG, Tumeurs Malignes Rares Gynécologiques.

REVISION QUESTIONS

1. What is the definition of a rare cancer?
2. What is the essential requirement for the diagnosis of rare gynaecological tumours?
3. Which type of organisation may help clinicians in the management of rare gynaecological tumours?

Some specific rare ovarian cancers

Therapeutic and diagnostic perspectives relative to rare diseases are changing with the advent of molecular profiling.

Clinical trials are evolving from 'one size fits all' to a personalised approach.

For example, the BOUQUET trial (NCT04931342) is designed to evaluate the efficacy and safety of biomarker-driven therapies in patients with persistent/recurrent rare epithelial gynaecological tumours.

ENGOT-GYN2/GOG-3051/BOUQUET trial (NCT04931342)

Pretreated or recurrent epithelial OC. Prescreening with NGS and pathology	
Target	**Treatment**
*PIK3CA** or *AKT** or *PTEN***	AKTi + paclitaxel
BRAF/KRAS*/NRAS** and/or *NF1***	MEKi
ERBB2 amplification and/or mutation	Anti-HER2 conjugated mAb
*PIK3CA** (without *AKT1** and *PTEN***)	PI3KCAαi + CDK4/6i
ER+ and *PIK3CA** (without *AKT1** and *PTEN***)	PI3KCAαi + CDK4/6i + AI
Non-matched (without *BRCA***)	PI3KCAαi + PARPi
ER+	SERD + CDK4/6i
Non-matched	Anti-PD-L1 + anti-VEGF

Fig. 10.4

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ER+, oestrogen receptor-positive; HER2, human epidermal growth factor receptor 2; i, inhibitor; mAb, monoclonal antibody; NF1, neurofibromin 1; NGS, next-generation sequencing; OC, ovarian cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PTEN, phosphatase and tensin homologue; SERD, selective oestrogen receptor degradation; VEGF, vascular endothelial growth factor.
*constitutive activation; **loss of function.

Female sex cord-stromal tumours and their key molecular alterations

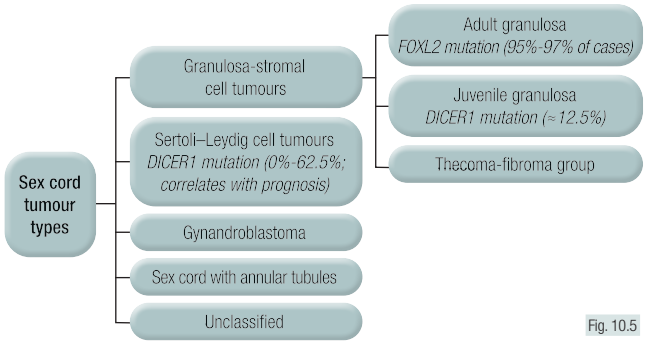


Fig. 10.5

Adult granulosa cell tumour is the most common type of sex cord-stromal tumour (SCST) (~70%), affecting patients aged 30–90 years and occasionally causing endocrine disturbances.

Detected at early stage, SCSTs have, overall, a good prognosis. Late recurrence appears in up to 30% of cases, requiring long-term follow-up. Surgery is the cornerstone of initial management.

For advanced/recurrent disease, BEP (bleomycin, etoposide and platinum) is the standard treatment, although response is often short-lived. Endocrine therapy (ET) is an option for indolent disease.

Malignant ovarian germ cell tumours (MOGCTs) (3% of ovarian cancers) occur predominantly in young women and children. Rapid diagnosis and treatment are required for these aggressive but curable cancers.

Fertility-sparing surgery is recommended for MOGCTs, as they are responsive to platinum-based chemotherapy (ChT). Tumour markers (e.g. AFP [alpha-foetoprotein], βHCG [beta-human chorionic gonadotropin]) are useful for diagnosis and surveillance.

In rare cases, a benign teratoma may become malignant, e.g. squamous cell carcinoma arising in a dermoid. These patients are challenging to manage if they have advanced-stage disease.

Main subtypes of female GCTs

Subtype	Frequency	Blood markers
Dysgerminoma	35%–45%	LDH and hCG
Endodermal sinus tumour (yolk sac)	20%	AFP (common) or α-1 antitrypsin (rare)
Teratoma (± mature)	20%	Immature: AFP, LDH, CA125
Mixed GCT	10%–20%	Dependent on cell types
Embryonal carcinoma	Rare	AFP and hCG
Polyembryoma	Rare	AFP and hCG
Choriocarcinoma	Very rare	hCG

Fig. 10.6

AFP, alpha-foetoprotein; CA125, cancer antigen 125; GCT, germ cell tumour; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

REVISION QUESTIONS

1. Which patients are eligible for conservative surgery?
2. Which blood markers are helpful in the diagnosis of rare ovarian cancers?
3. Which rare gynaecological tumours do not respond to ChT?

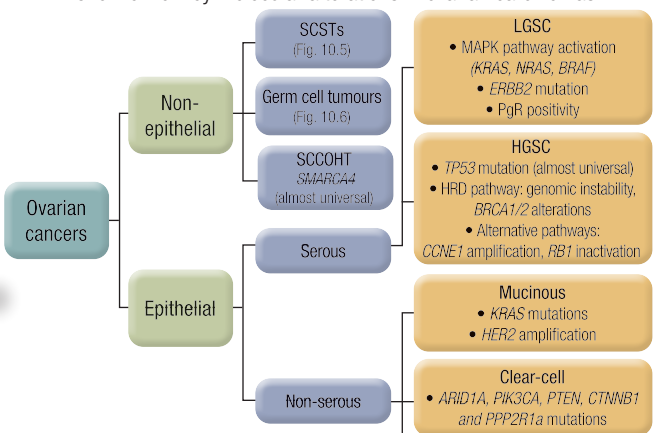
Focus on selected subtypes; molecular biology

Some serous borderline ovarian tumours share molecular patterns with low-grade serous carcinoma (LGSC) but have no infiltration or stromal invasion. They affect young patients, typically at localised stage.

LGSCs present at advanced stage (FIGO III/IV) in younger patients (40–50 years) and are generally chemoresistant; surgery is the mainstay of management. Anti-oestrogen and MEK inhibitor treatments may control residual/recurrent disease.

Advanced mucinous ovarian cancer (MOC) is very rare, chemoresistant and has a poor prognosis. Stage IA MOC is more common, occurring in young women and cured by surgery.

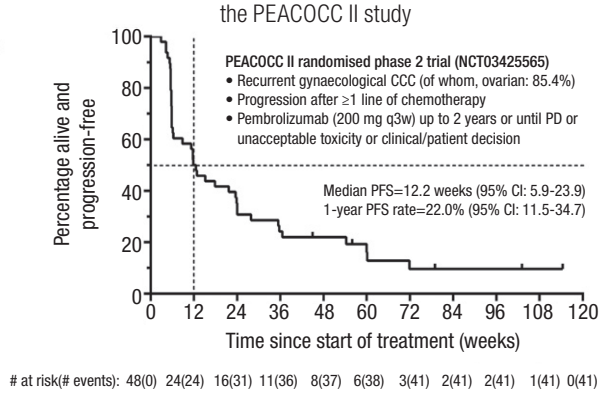
Overview of key molecular alterations in ovarian carcinomas



HER2, human epidermal growth factor receptor 2; HGSC, high-grade serous carcinoma; HRD, homologous recombination deficiency; LGSC, low-grade serous carcinoma; MMR, mismatch repair; PgR, progesterone receptor; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma 1; SCCOHT, small cell carcinoma of the ovary, hypercalcaemic type; SCST, sex cord-stromal tumour.

Fig. 10.7

Pembrolizumab in advanced clear cell gynaecological cancer: the PEACOCC II study



CCC, clear cell carcinoma; CI, confidence interval; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks.

Fig. 10.8

Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) is very aggressive and characterised by *SMARCA4* mutation. Optimal management is multimodal: surgery, ChT and adjuvant radiotherapy (RT).

Ovarian clear cell carcinomas (CCCs) are more frequent in Asian populations and may arise from endometriosis. Surgery is important as most are chemoresistant. Programmed cell death protein 1 (PD-1) inhibitors show promise in controlling recurrent disease.

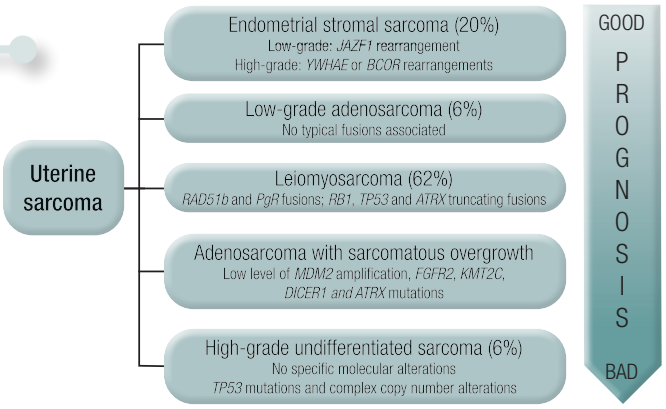
Undifferentiated uterine sarcomas are highly aggressive diseases, mainly affecting the elderly. Surgery and carboplatin-based ChT are standard treatments.

Endometrial stromal sarcomas are usually low-grade, hormone receptor-positive (80%-95% of cases); with t(7;17)(p15;q21) in 60%. Surgery is sufficient for most; relapse occurs 8–20 years later and ET is useful.

Leiomyosarcoma is very aggressive, with poor prognosis. RT minimises pelvic recurrence but has no effect on overall survival (OS). ChT has modest activity in the recurrent/metastatic setting.

High-grade undifferentiated uterine sarcoma is an aggressive disease mainly affecting the elderly, always oestrogen receptor/progesterone receptor (ER/PgR)-negative; t(10;17) translocation in 30%. OS ranges from 12 to 23 months (even for early stage).

Mesenchymal uterine cancers: sarcomas



FGFR2, fibroblast growth factor receptor 2; PgR, progesterone receptor; RB1, retinoblastoma 1.

Fig. 10.9

REVISION QUESTIONS

1. Which are the two druggable pathways involved in the pathogenesis of LGSCs?
2. What is the current role of immunotherapy in the management of rare gynaecological tumours?
3. What is the cornerstone of endometrial stromal sarcoma management?

Summary: Rare gynaecological cancers

- Any gynaecological cancer should be anticipated as possibly rare, since rare cancers account for more than 50% of gynaecological cancers
- The first step in diagnosis includes clinical examination, identification of markers and imaging data
- Pathological analysis must include a review by an expert pathologist for confirmation, and further molecular explorations if needed. Discordance in diagnosis is frequent
- Molecular biology is increasingly used to define tumour subtype, to drive oncogenetic and targeted treatments
- Quality of surgery for staging or for treatment should be evaluated by multidisciplinary experts. Tumour rupture or morcellation are key pointers for worse prognosis, compared with complete surgery
- Fertility-sparing surgery is an acceptable option for young women (MOGCTs, sex cord or borderline tumours)
- Adjuvant treatment with ChT is based on histology, staging, postoperative residue and prognostic factors
- The development of new diagnostic resources to define new specific entities is ongoing. Each rare tumour subtype suffers from a lack of knowledge regarding oncogenesis, diagnosis and treatment
- Centralisation of data, networking and international collaboration are urgently needed to support dedicated translational research and randomised clinical trials, to improve knowledge on management and prognosis in these patients

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11 Hereditary ovarian and uterine cancer syndromes

Genetic basis

Most cancers have chromosomal abnormalities, both in number and in structure, whereas some show only a single aberration.

Evidence from the recent molecular era indicates that cancers can arise from a small number of events that affect common cell birth and death processes.

Knudson suggested that two 'hits' to DNA were necessary to silence both alleles and cause cancer.

Two-hit theory of cancer causation

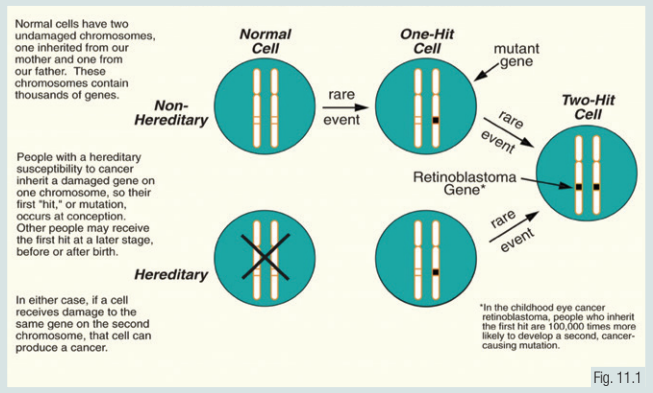


Fig. 11.1

Autosomal-dominant inheritance

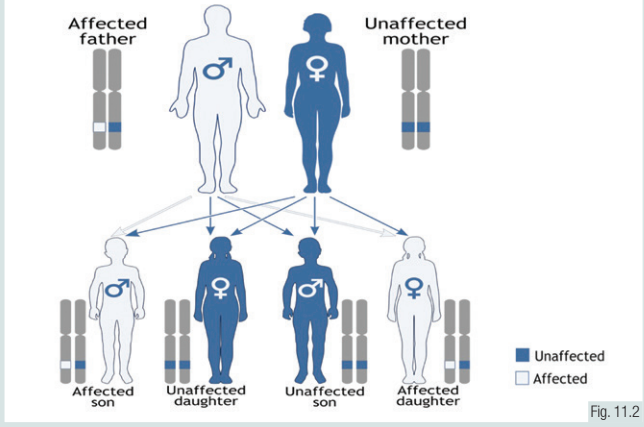


Fig. 11.2

Autosomal-dominant inheritance is a genetic inheritance pattern where an abnormal gene (inherited from one parent) is dominant over the normal gene (inherited from the other parent).

The individual shows the characteristics associated with the abnormal gene, e.g. high risk of cancer.

Hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS, also referred to as hereditary non-polyposis colorectal cancer [HNPCC]) and Li–Fraumeni syndrome follow an autosomal dominant inheritance pattern.

BRCA1, *BRCA2* and other genes related to homologous recombination maintain genomic integrity. Mutations in these genes cause genome instability and HBOC syndrome.

Mutations in the DNA mismatch repair (MMR) genes result in DNA replication errors known as microsatellite instability (MSI). LS predisposes for endometrial (EC), ovarian (OC), colorectal and many other types of cancer.

These deleterious germline mutations causing homologous recombination or MMR deficiency can also occur as somatic mutations in cancer but are then not inheritable.

Mutations in HBOC and Lynch syndrome

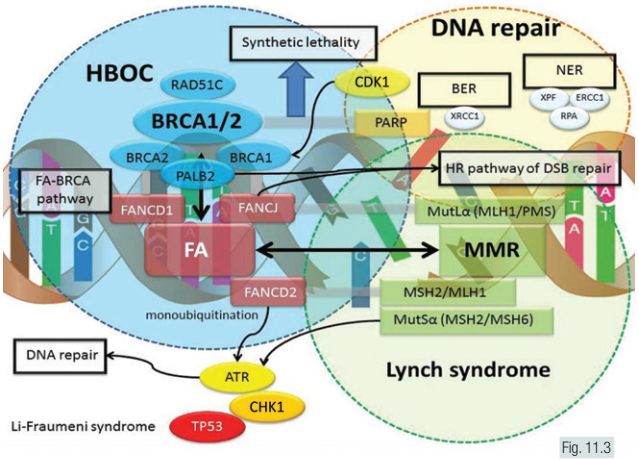


Fig. 11.3

CDK1, cyclin-dependent kinase 1; CHK1, checkpoint kinase 1; DSB, double-strand break; FA, Fanconi anaemia; HBOC, hereditary breast and ovarian cancer; HR, homologous recombination; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase.

REVISION QUESTIONS

1. What is the 'two-hit' theory?
2. What are the most important genes predisposing to OC and EC?
3. Why are mutations in *BRCA1* or *BRCA2* associated with cancer?

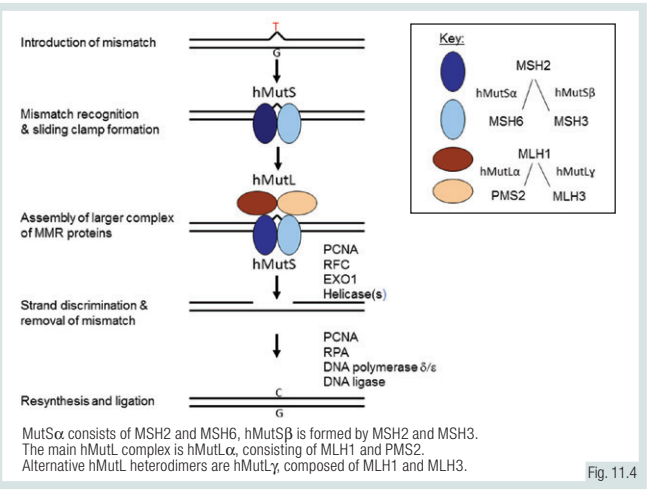
Genetic predisposition

Mismatches and small insertion-deletion loops (IDLs) are detected by one of two heterodimers, MutSα or MutSβ, followed by the recruitment of MutLα heterodimer.

When this complex recognises a strand discontinuity, the excision machinery is recruited, degrading the mismatch fragment and synthesising a new strand.

The repair process requires several other proteins, such as proliferating cell nuclear antigen (PCNA), replication factor C (RFC) or DNA polymerases.

DNA mismatch repair (MMR)



MutSα consists of MSH2 and MSH6, hMutSβ is formed by MSH2 and MSH3. The main hMutL complex is hMutLα, consisting of MLH1 and PMS2. Alternative hMutL heterodimers are hMutLγ, composed of MLH1 and MLH3.

Fig. 11.4

PCNA, proliferating cell nuclear antigen; RFC, replication factor C.

Genetic predisposition to cancer

Syndrome	Primary cancers	Associated neoplasms	Genes
Hereditary breast & ovarian cancer syndrome (HBOC)	Breast, ovary	Pancreas, male breast, prostate, stomach, thyroid, gallbladder	*BRCA1, BRCA2, RAD51C, RAD51D, CHEK2, PALB2*
Peutz–Jeghers syndrome	Colon, oesophagus, stomach	Small intestine, pancreas, lung, breast, uterus, ovary	*STK11/LKB1*
Cowden syndrome	Breast, thyroid, endometrium	Ovary	*PTEN*
Li–Fraumeni syndrome	Breast, sarcomas, CNS, leukaemia, adrenocortical	Tumours in many sites	*TP53*
Lynch syndrome (HNPCC)	Colon, endometrium	Ovary, small intestine, oesophagus, ureter, renal pelvis, glioblastoma	MMR gene: *MLH1, MSH2, MSH6, PMS1, PMS2, EPCAM*

CHEK2, checkpoint kinase 2; CNS, central nervous system; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair; PTEN, phosphatase and tensin homologue.

Fig. 11.5

Inherited mutations play a major role in the development of approximately 5%–10% of all cancers.

Genetic mutations associated with more than 50 hereditary cancer syndromes have been identified, and genetic tests can help tell whether a person from an affected family has inherited one of these mutations.

LS is caused by heterozygous germline loss-of-function mutations of the genes encoding the crucial components of the MMR system (*MLH1, MSH2, MSH6* or *PMS2*).

A woman's lifetime risk of developing OC is greatly increased if she inherits a harmful mutation in *BRCA1 or BRCA2*.

By the age of 70 years, women with a harmful *BRCA1* or *BRCA2* mutation have a risk of 39%–44% and 11%–17%, respectively, for developing OC.

Men carrying *BRCA1/2* harmful mutations have a lower incidence of cancers, but their female offspring will have a 50% chance of inheritance.

BRCA mutation and hereditary cancer risk

	BRCA1	*BRCA2*
Breast cancer (females)	55%–85%	45%–84%
Ovarian cancer	39%–44%	11%–17%
Cowden syndrome	Low	6%
Prostate cancer*	-	9%

**BRCA1* gene mutation may slightly increase the risk of developing prostate cancer before the age of 65; however, the evidence is insufficient.

Fig. 11.6

REVISION QUESTIONS

1. What is the mechanism of action of MMR genes?
2. How frequent are inherited mutations a cause for gynaecological cancer?
3. What are the criteria for a person to have HBOC?

Screening and surveillance

LS increases the risk of several gynaecological malignancies (endometrial, ovarian and ureter).

In women with LS, the risk for developing EC exceeds colorectal cancer, with >50% of first-arising 'sentinel' tumour cases being gynaecological tumours.

Diagnosis of LS is possible only by mutation analysis. In patients affected with typical LS tumours, immunohistochemical screening for loss of MMR proteins should be performed and, if observed, genetic counselling and analysis offered.

Extracolonic tumours associated with Lynch syndrome/HNPCC

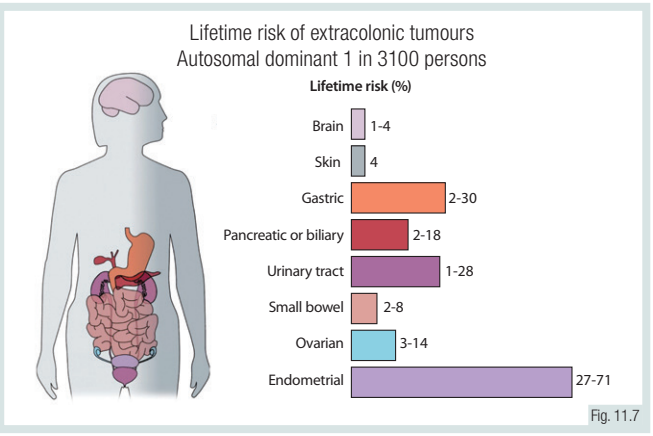


Fig. 11.7

HNPCC, hereditary non-polyposis colorectal cancer.

Immunohistochemical testing for MMR deficiency in all patients with EC

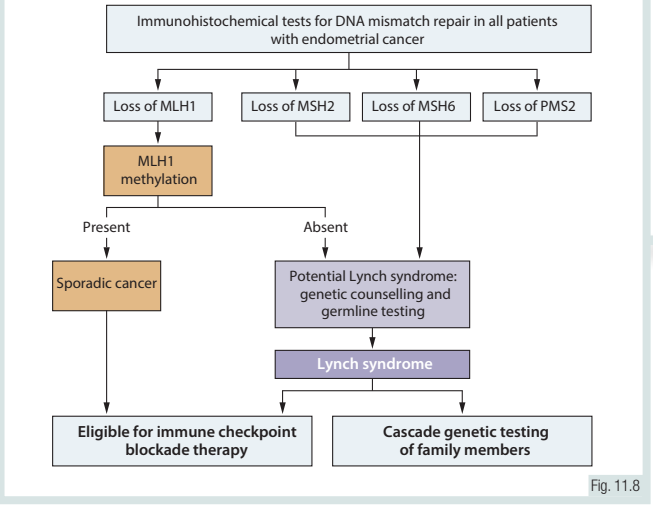


Fig. 11.8

EC, endometrial cancer; MMR, mismatch repair.

Criteria such as Amsterdam II, Modified Bethesda or the Society of Gynecologic Oncology criteria have been published to guide screening and testing.

All ECs should be tested for MMR deficiency using MMR immunohistochemistry (IHC) followed by reflex MLH1 methylation testing.

Tumour-based testing identifies individuals who should undergo definitive germline testing (10%). LS can be detected in 3% of EC patients.

For patients with LS, the only surveillance which has demonstrated a beneficial effect is colonoscopy starting at young age; unfortunately, there is no clear evidence for the screening of gynaecological malignancies.

Healthy female carriers of LS can reduce their EC risk through prophylactic hysterectomy when they have completed their family.

Prophylactic bilateral salpingo-oophorectomy in *BRCA* mutation-carriers lowers OC risk by >90%.

Surveillance for Lynch syndrome carriers

Cancer	Intervention	Recommendation	Institution	Evidence
Colon	Colonoscopy	From age 20–25 y or 5 y prior to the youngest age at which a family member first had colorectal cancer, repeat annually or biennially	NCCN/ AWMF	+++
Endometrium	Endometrium biopsy (Pipelle)	From age 35 y, annually (optional, no clear evidence)	AWMF NCCN	-
Endometrium	Transvaginal ultrasound	From age 35 y, annually (optional, no clear evidence)	AWMF NCCN	-
Ovary	Transvaginal ultrasound +/- CA125	From age 25 y, annually (optional, no clear evidence	AWMF NCCN	-
Urothelium/ bladder	Urinalysis	From age 25–30 y, annually (optional, no clear evidence)	NCCN	-
CNS	Physical/neurological examination	From age 25–30 y (optional, no clear evidence)	NCCN	-
Gastric	Gastroscopy	From age 30–35 y, every 3–5 y	NCCN/ AWMF	+/-

AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; CA125, cancer antigen 125; CNS, central nervous system; NCCN, National Comprehensive Cancer Network; y, years.

Fig. 11.9

REVISION QUESTIONS

1. How is a diagnosis of LS made?
2. Which cancer types are associated with LS?
3. What strategies do you know for cancer prevention in women with harmful mutation in *BRCA1* or *BRCA2* or mutations in MMR genes?

Summary: Hereditary ovarian and uterine cancer syndromes

- Approximately 5%–10% of cancers arise due to inherited mutations in genes
- Two manifestations of hereditary OC are currently recognised: HBOC syndrome and HNPCC syndrome
- A woman's lifetime risk of developing breast cancer, OC or EC is greatly increased if she inherits a harmful mutation in *BRCA1* or *BRCA2* or mutation in MMR genes
- HNPCC, also known as LS, has been defined clinically and genetically and is an autosomal-dominant cancer predisposition syndrome
- Patients with LS-associated malignancies including colorectal, endometrial, stomach, ovarian, pancreatic, ureter and renal pelvis, biliary tract and glioblastoma have an improved outlook
- All ECs should be tested for MMR deficiency using MMR IHC followed by reflex MLH1 methylation testing
- For gynaecological cancer surveillance in healthy LS patients, transvaginal ultrasound plus endometrial biopsy and cancer antigen 125 (CA125) measurements may be considered
- Prophylactic surgery is another appropriate option for individuals carrying harmful *BRCA* mutations and LS

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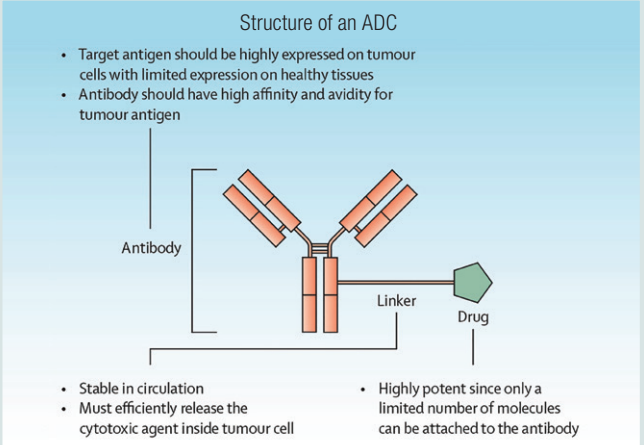
12 New drugs and novel treatment strategies for gynaecological cancers

Antibody–drug conjugates

Antibody–drug conjugates (ADCs) are a novel class of agents with a unique structure comprising a monoclonal antibody (mAb) conjugated to a potent chemotherapy (ChT) agent (payload) through a linker.

ADCs have been developed to enable targeted delivery of highly cytotoxic agents to cancer cells, with limited off-target systemic effects.

The conjugated drug may also affect cancer cells with low or absent antigen expression (bystander effect), particularly when cleavable linkers or hydrophobic payloads are used.



ADC, antibody–drug conjugate. Fig. 12.1

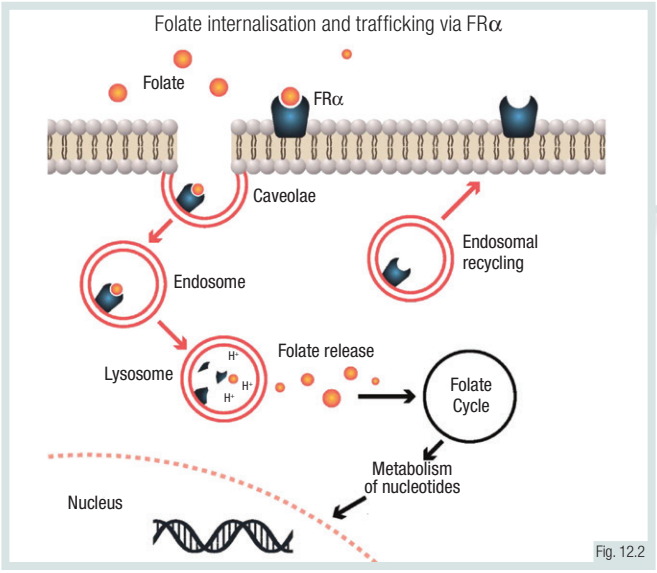


Fig. 12.2

FRα, folate receptor alpha.

Folate receptor alpha (FRα) is frequently overexpressed in ovarian cancer (OC), with limited expression in non-cancer cells.

Mirvetuximab soravtansine is an anti-FRα ADC that was tested in the phase III MIRASOL trial in patients with high FRα platinum-resistant OC and showed a clear benefit.

In cervical cancer (CC), the anti-tissue-factor ADC tisotumab vedotin was shown to improve overall survival as a single agent in second line and promising activity in combination.

Other targets of interest are: sodium-dependent phosphate transporter 2b (NaPi2b), mesothelin, trophoblast cell-surface antigen 2 (Trop-2), MUC16, human epidermal growth factor receptor 2 (HER2) and cadherin 6 (CDH6).

HER2 overexpression occurs in ~35% of endometrial cancers (ECs) and HER2-targeting ADCs may represent a promising treatment option; trials are ongoing.

Different mechanisms of resistance to ADCs have been identified, including heterogeneous antigen expression, extracellular payload release or altered intracellular trafficking.

Main ADCs under investigation in gynaecological malignancies

Target	ADC	Antibody	Linker	Payload	DAR
FRα	Mirvetuximab soravtansine	IgG1-kappa	Cleavable	DM4	3–5
	MORAb-202	IgG1-kappa	Cleavable	Eribulin	4
	Luveltamab tazevibulin	IgG1	Cleavable	Hemiasterlin	2
Tissue factor	Tisotumab vedotin	IgG1-kappa	Cleavable	MMAE	4
NaPi2b	Lifastuzumab vedotin	IgG1	Cleavable	MMAE	10–15
	Upifitamab rilsodotin	IgG1	Cleavable	Auristatin	~10
HER2	Trastuzumab emtansine	IgG1	Non-cleavable	DM1	3.5
	Trastuzumab deruxtecan	IgG1	Cleavable	Deruxtecan	7–8
Trop-2	Sacituzumab govitecan	IgG1-kappa	Cleavable	SN38	7.6
	Datopotamab deruxtecan	IgG1	Cleavable	Deruxtecan	4

Fig. 12.3

ADC, antibody–drug conjugate; DAR, drug–antibody ratio; FRα, folate receptor alpha; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; MMAE, monomethyl auristatin E; NaPi2b, sodium-dependent phosphate transporter 2b; Trop-2, trophoblast cell-surface antigen 2.

REVISION QUESTIONS

1. What are the main elements of an ADC?
2. Which features of an ADC support a bystander effect?
3. Which are the main ADCs under investigation in gynaecological malignancies?

Targeting the DNA damage response beyond PARP inhibitors

The DNA damage response (DDR) is a network of pathways activated in response to DNA damage and represents the coordinated activity of the DNA repair and cell cycle checkpoints.

Generation of aberrant fork structures with single-stranded DNA activates the replication stress response with phosphorylation of ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), promoting cell survival.

Defects in DDR induce genome instability, leading to cancer initiation and progression, but also represent a vulnerability that can be exploited therapeutically.

Main components of the DDR pathway and their inhibitors

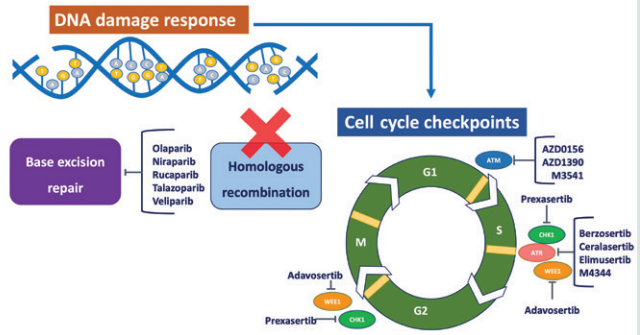


Fig. 12.4

ATR, ataxia telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; DDR, DNA damage response.

Main trials of adavosertib in gynaecological cancers

Treatment	Cancer type	N	Efficacy
Adavosertib + carboplatin (Leijen et al)	PROC	24	ORR: 43% PFS: 5.3 mo
Adavosertib or placebo + carboplatin/paclitaxel (Oza et al)	PSOC	121	ORR: 74.6% vs 69.9% (p = 0.52) PFS: 9.9 vs 8 mo (HR: 0.55)
Adavosertib or placebo + gemcitabine (Lheureux et al)	PROC	99	ORR: 23% vs 6% (p = 0.038) PFS: 4.6 vs 3 mo (HR: 0.55)
Adavosertib or adavosertib + olaparib (Westin et al)	PARPi resistant OC	35 (each)	ORR: 23%, PFS: 5.3 mo ORR: 29%, PFS: 6.8 mo
Adavosertib + chemotherapy (Moore et al)	PROC	94	ORR: 32% PFS 5.5 mo
Adavosertib (Au-Yeung et al)	PROC cyclin E-pos	32	ORR: 53%
Adavosertib (Liu et al)	USC	34	ORR: 29.4% PFS: 6.1 mo

Fig. 12.5

HR, hazard ratio; mo, months; OC, ovarian cancer; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression free survival; pos, positive; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; USC, uterine serous carcinoma.

Inhibitors of cell cycle checkpoints (ATM, ATR, WEE1 or checkpoint kinase 1 [CHK1]) have been investigated in gynaecological malignancies, either as single agents or in combination with ChT or poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis).

The WEE1 inhibitor adavosertib is the most studied, and promising results have been reported in patients with OC and EC.

Haematological toxicity remains one of the major obstacles in the development of these agents when used both as single agents and, above all, in combination strategies.

The PARP family consists of 17 PARP proteins with a conserved domain catalysing the transfer of ADP ribose to target proteins or nucleic acids (parylation).

PARP1 and PARP2 are the best characterised and the targets for first-generation PARPis; there are differences between agents with respect to PARP trapping, selectivity and pharmacology.

The next-generation highly selective PARP1 inhibitor AZD5305 has demonstrated higher potency and better tolerability than first-generation PARPis and early-phase trials are ongoing.

PARPi activity across different PARP enzymes

	Olaparib	Rucaparib	Niraparib	Talazoparib
PARP1	1 - 19 nM	0.8 - 3.2 nM	2 - 35 nM	0.6 - 1.1 nM
PARP2	1 - 251 nM	28.2 nM	2 - 15.3 nM	4.1 nM
PARP3	46 - 230 nM	512 nM	296 - 1,300 nM	62.8 nM
PARP4	410 nM	839 nM	330 - 446 nM	254 nM
TNKS1	1,230 - 3,534 nM	25 - 144 nM	570 - 2,355 nM	322 nM
TNKS2	1,700 - 2,340 nM	14 - 890 nM	5,130 nM	108 nM
PARP10	1,250 - 9,300 nM	570 nM	1,900 nM	7,800 nM
PARP12	10,050 nM	6,650 nM	790 nM	
PARP14		8,830 nM	17,300 nM	25,500 nM
PARP15	17,600 nM	32,600 nM	29,200 nM	47,400 nM
PARP16	5,100 nM			1,900 nM

Literature IC_{50} values

1-10 nM · 10-100 nM · 100-1,000 nM · 1,000-10,000 nM · Weak inhibition (> 10,000 nM) · No inhibition · Not determined

Fig. 12.6

IC_{50}, half maximal inhibitory concentration; nM, nanomolar; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor.

REVISION QUESTIONS

1. What is the main role of the DDR?
2. In which settings has the WEE1 inhibitor adavosertib been investigated?
3. What is the major toxicity observed with DDR inhibitors?

Combinations with DDR-targeting agents

Mitigation of replication stress via activation of cell cycle checkpoints and stabilisation of replication forks is one of the mechanisms of PARPi resistance.

Novel combinations of DDR inhibitors (DDRis) or inhibitors of oncogenic drivers or survival pathways have been assessed to overcome intrinsic or acquired PARPi resistance.

Despite strong biological rationale and preclinical efficacy, combinations of PARPis with other DDRis are challenged by overlapping toxicity profiles.

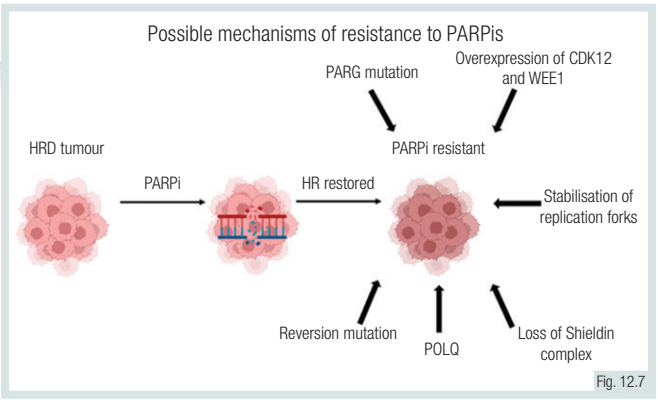


Fig. 12.7

CDK12, cyclin-dependent kinase 12; HR, homologous recombination; HRD, homologous recombination deficiency; PARG, poly (ADP-ribose) glycohydrolase; PARPi, poly (ADP-ribose) polymerase inhibitor; POLQ; polymerase θ.

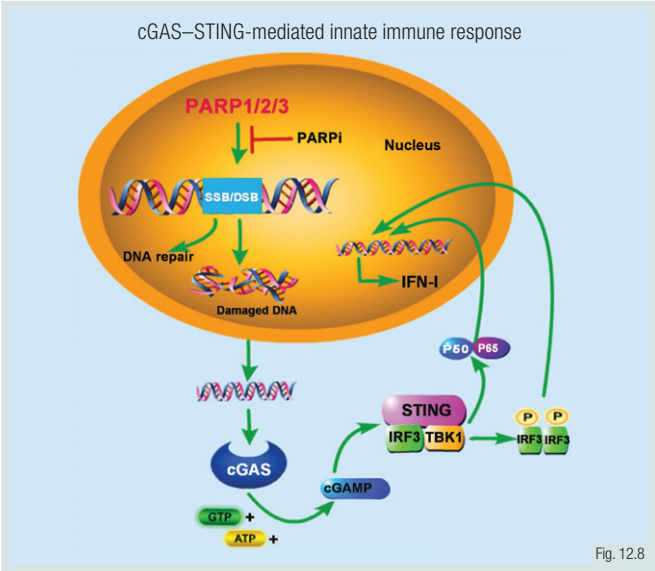


Fig. 12.8

ATP, adenosine triphosphate; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; DSB, double-strand break; GTP, guanosine triphosphate; IFN-1, interferon 1; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; SSB, single-strand break; STING, stimulator of interferon genes.

Inhibiting DDR pathways stimulates antitumour immunity, providing the biological rationale to combine DDRis and immune checkpoint inhibitors (ICIs).

PARPis upregulate programmed death-ligand 1 (PD-L1), release DNA fragments that activate a stimulator of interferon genes (STING) innate immune response and may increase the level of neoantigens.

Combinations of ICIs (anti-programmed cell death protein 1 [PD-1]/PD-L1 or anti-cytotoxic T-lymphocyte antigen 4 [CTLA-4]) and PARPis are under investigation in OC, including first-line and recurrence settings.

Histone deacetylase inhibitors (HDACis), bromodomain and extraterminal inhibitors (BETis), and enhancer of zeste homologue 2 inhibitors (EZH2is) can induce epigenetic modifications.

HDACis, BETis and EZH2is reduce the expression of genes involved in homologous recombination and cell cycle control and are being investigated in combination with PARPis.

Phosphoinositide-3 kinase (PI3K) inhibitors downregulate the expression of *BRCA*, inducing a homologous recombination deficiency (HRD) phenotype; alpelisib has shown synergist effect with olaparib in preclinical models of OC.

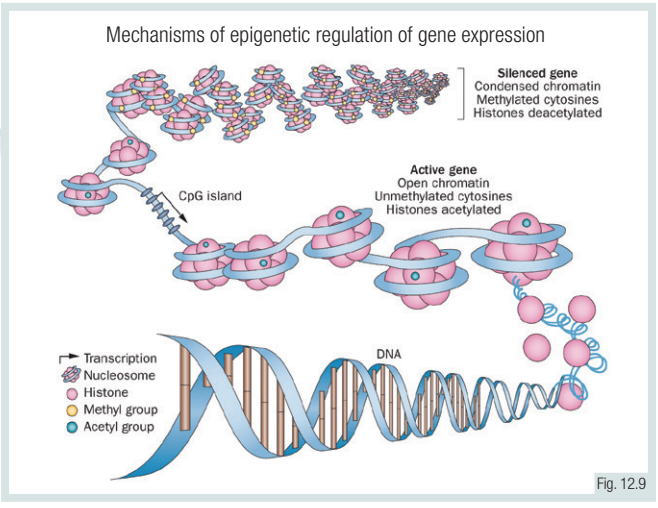


Fig. 12.9

REVISION QUESTIONS

1. What is the main challenge of combining different DDRis?
2. What are the mechanisms of PARPi-induced immune response?
3. What is the mechanism of action of HDACis and BETis?

Novel immunotherapy approaches

TIGIT (T-cell immunoreceptor with Ig [immunoglobulin] and ITIM [immunoreceptor tyrosine-based inhibitory motif] domains) is another immune checkpoint receptor that is emerging as a therapeutic target.

TIGIT is expressed on most natural killer (NK) cells and other subsets of T cells, including regulatory T cells (Tregs), memory and activated T cells and T helpers.

TIGIT inhibits cytotoxic activity, degranulation and cytokine secretion of NK cells by binding to the poliovirus receptor (PVR), a key regulator of cell-mediated immunity.

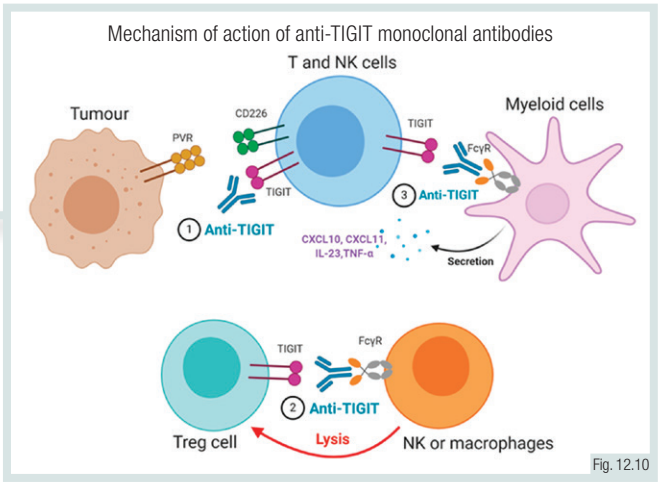
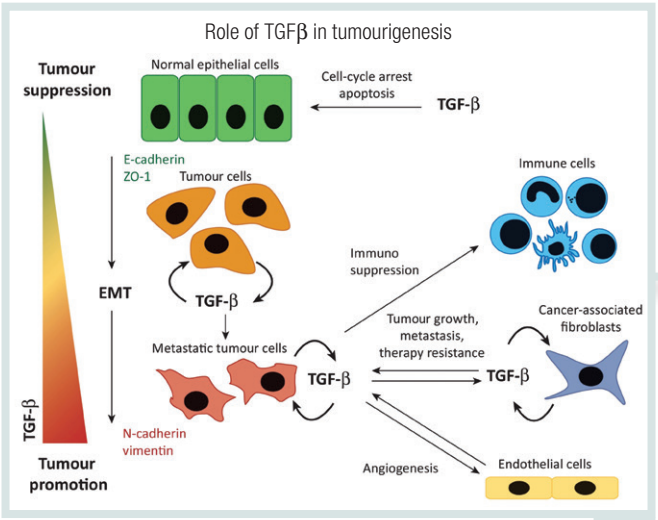


Fig. 12.10

FcγR, fragment crystallisable gamma receptor; IL-23, interleukin-23; NK, natural killer; PVR, poliovirus receptor; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains; TNF-α, tumour necrosis factor alpha; Treg, regulatory T cell.



EMT, epithelial–mesenchymal transition; TGFβ, transforming growth factor beta.

Fig. 12.11

In CC, the human papillomavirus (HPV) E6 and E7 oncoproteins can increase the expression of immunosuppressive cytokines, including transforming growth factor beta (TGFβ).

TGFβ overexpression sustains tumourigenesis through activation of epithelial–mesenchymal transition (EMT), fibroblast activation, angiogenesis and immunosuppression.

High levels of TGFβ are associated with resistance to immunotherapy and its inhibition has been shown to increase the activity of anti-PD-1/PD-L1 agents.

Combinations of ICIs (anti-PD-1/PD-L1 + anti-CTLA-4 and bispecific antibodies) have shown promising results in gynaecological malignancies.

Therapeutic DNA vaccines against HPV have shown signs of activity, particularly when combined with anti-PD-1/PD-L1 agents in CC.

Combinations of immunotherapy agents with ChT and antiangiogenics have recently been shown to improve outcomes for patients with CC and EC.

New immunotherapy agents under investigation in CC

Compound	Structure	MoA	Target tumour	Ongoing studies
Bintrafusp alfa (M7824)	Bifunctional fusion protein of extracellular domain of TGFβ RII receptor and human anti-PD-L1 mAb	TGFβ trap + anti-PD-L1	Advanced, recurrent, metastatic CC after failure of platinum ChT HPV-associated malignancies	Phase II single agent
Tiragolumab	Humanised IgG1 kappa mAb	TIGIT binding to prevent interaction with PVR ligand	PD-L1 positive recurrent, metastatic CC after failure of up to 2 lines of prior ChT	Phase II randomised atezolizumab ± tiragolumab
Cadonilimab (AK104)	IgG1 scaffold Fc-engineered humanised antibody	Anti-PD-1/CTLA-4 bispecific Ab	Persistent, recurrent, metastatic CC; no prior ChT	Phase III AK104/placebo + platinum and paclitaxel ± bevacizumab
Balstilimab (AGEN1884) + zalifrelimab (AGEN1884)	Humanised IgG4 mAb Humanised IgG1 mAb	Anti-PD-1 + anti-CTLA-4	Persistent, recurrent, metastatic CC after failure of first-line ChT	Randomised non-comparative phase II
Tirvalimogene (GX-188E) + pembrolizumab	Therapeutic DNA vaccine-encoding E6/E7 fusion proteins of HPV16 and HPV18	Elicits cytotoxic T-cell response against E6-E7 expressing cells	Recurrent/advanced HPV16- or HPV18-positive CC	Phase II single arm

Fig. 12.12

Ab, antibody; CC, cervical cancer; ChT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte antigen 4; Fc, fragment crystallisable; HPV, human papillomavirus; Ig, immunoglobulin; mAb, monoclonal antibody; MoA, mechanism of action; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PVR, poliovirus receptor; TGFβ, transforming growth factor beta; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains.

REVISION QUESTIONS

1. Which are the new promising immunotherapy targets under investigation?
2. What is the main role of TGFβ?
3. Where is TIGIT expressed?

New pathways of interest

The tyrosine kinase receptor AXL and its ligand growth arrest-specific 6 (GAS6) are implicated in different cancer cell functions and are a new potential target in OC.

The AXL/GAS6 pathway is involved in tumour cell proliferation and invasion, EMT, angiogenesis, immunosuppression and drug resistance.

In many human cancers, including OC, the aberrant expression of AXL/GAS6 has been associated with poor prognosis and shorter survival.

The AXL/GAS6 pathway and its functions

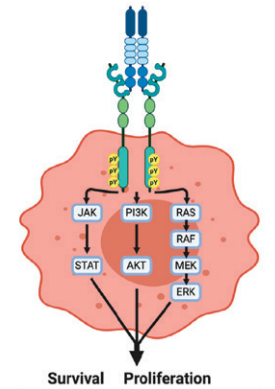


Fig. 12.13

ERK, extracellular signal-regulated kinase; GAS6, growth arrest-specific 6; JAK, Janus kinase; PI3K, phosphoinositide-3 kinase.

Mechanism of XPO1-mediated nuclear export

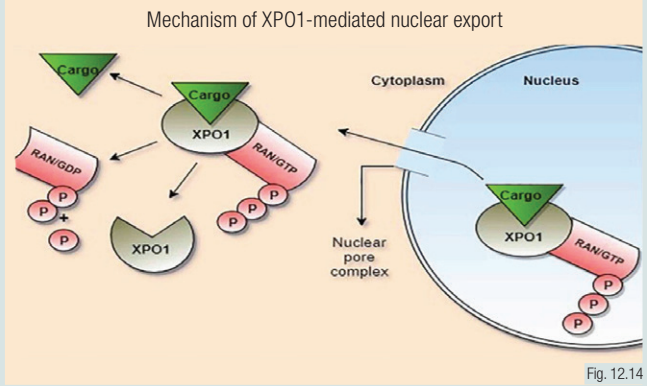


Fig. 12.14

GDP, guanosine diphosphate; GTP, guanosine triphosphate; P, phosphate; RAN, ras-related nuclear protein; XPO1, exportin 1.

XPO1 (exportin 1) is responsible for the transport from the nucleus to the cytoplasm of over 200 proteins, including tumour-suppressor proteins and oncoproteins.

Among XPO1-mediated proteins are p53, FOXOs, p27, p21, nuclear-factor kappa B (NF-κB) and retinoblastoma (Rb), which are functionally inactivated upon cytoplasmic export, resulting in tumour-promoting effects.

XPO1 overexpression has been demonstrated in many solid tumours and haematological malignancies and is associated with poor prognosis and drug resistance.

Targeting AXL can increase the efficacy of ChT and epidermal growth factor receptor (EGFR), PI3K, PARP and HER2 inhibitors.

AXL/GAS6-targeted therapies include small molecule inhibitors, mAbs, nucleotide aptamers and soluble receptors.

Selinexor is an oral first-in-class selective inhibitor of nuclear export (SINE) compound and is under investigation in different solid tumours, including EC.

New agents under investigation in gynaecological cancers

Compound	Structure	MoA	Target tumour	Ongoing studies
EP0057	Nanoparticle–drug conjugate with camptothecin	Cytotoxicity	PROC	Phase II in combination with olaparib
AVB-S6-500 (batiraxcept)	Fusion protein of modified extracellular portion of human AXL with Fc IgG1	Trapping of GAS6	PROC	Phase III randomised ± paclitaxel
BA3011 (mecbotamab vedotin)	Conditionally active biologic with MMAE	Anti-AXL mAb	PROC, HGSC	Phase II + durvalumab (immunotherapy platform study)
Selinexor	Oral small molecule inhibitor	Inhibition of XPO1	Recurrent/metastatic endometrial cancer	Phase III randomised double-blind as maintenance treatment following response to platinum-based ChT

Fig. 12.15

ChT, chemotherapy; Fc, fragment crystallisable; GAS6, growth arrest-specific 6; HGSC, high-grade serous carcinoma; IgG1, immunoglobulin G1; mAb: monoclonal antibody; MMAE, monomethyl auristatin E; MoA, mechanism of action; PROC, platinum-resistant ovarian cancer; XPO1, exportin 1.

REVISION QUESTIONS

1. What are the main functions of the AXL/GAS6 pathway?
2. Which AXL-/GAS6-targeting agents are under investigation?
3. What is the function of XPO1?

Summary: New drugs and novel treatment strategies for gynaecological cancers

- ADCs are a new class of drugs that combine the targeting ability of a mAb with the cytotoxicity of a ChT agent
- Different ADCs have shown signs of activity in gynaecological malignancies and the more promising targets are FRα, Trop-2, NaPi2b, HER2 and tissue factor
- Although theoretically the addition of cell-cycle checkpoint inhibitors such as ATR, WEE1 and CHK1 could overcome PARPi resistance, overlapping haematological toxicity has limited their use in combination
- Selective inhibitors of PARP1 are being developed, with a promising safety profile that may increase the possibility for combination treatments
- PARPis stimulate immune responses through a variety of different mechanisms; combinations with ICIs have shown synergism
- TIGIT and TGFβ are new immunomodulatory targets and their inhibition may overcome resistance to anti-PD-1/PD-L1 agents
- The AXL/GAS6 pathway is involved in different cancer cell functions and its activation is associated with resistance and poor prognosis
- XPO1 transports different nuclear proteins, including tumour suppressors such as p53, into the cytoplasm, leading to oncogenic activation
- Selinexor is the first SINE under investigation in gynaecological malignancies, and signs of activity have been reported in EC

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Appendix 1: WHO Classification of Female Genital Tumours, 5th Edition, Volume 4

Tumours of the ovary

Serous tumours

- Benign serous tumours
  - Serous cystadenoma, adenofibroma, and surface papilloma
- Borderline serous tumours
  - Serous borderline tumour
- Malignant serous tumours
  - Low-grade serous carcinoma
  - High-grade serous carcinoma

Mucinous tumours

- Benign mucinous tumours
  - Mucinous cystadenoma and adenofibroma
- Borderline mucinous tumours
  - Mucinous borderline tumour
- Malignant mucinous tumours
  - Mucinous carcinoma

Endometrioid tumours

- Benign endometrioid tumours
  - Endometrioid cystadenoma and adenofibroma
- Borderline endometrioid tumours
  - Endometrioid borderline tumour
- Malignant endometrioid tumours
  - Endometrioid carcinoma

Clear cell tumours

- Benign clear cell tumours
  - Clear cell cystadenoma and adenofibroma
- Borderline clear cell tumours
  - Clear cell borderline tumour
- Malignant clear cell tumours
  - Clear cell carcinoma

Seromucinous tumours

- Benign seromucinous tumours
  - Seromucinous cystadenoma and adenofibroma
- Borderline seromucinous tumours
  - Seromucinous borderline tumour
- Malignant seromucinous tumours
  - Seromucinous carcinoma

Brenner tumours

- Benign Brenner tumours
  - Brenner tumour
- Borderline Brenner tumours
  - Borderline Brenner tumour
- Malignant Brenner tumours
  - Malignant Brenner tumour

Other carcinomas

- Mesonephric-like adenocarcinoma
- Undifferentiated and dedifferentiated carcinomas
- Carcinosarcoma
- Mixed carcinoma

Mesenchymal tumours

- Endometrioid stromal sarcoma
- Smooth muscle tumours
- Ovarian myxoma
- Other ovarian mesenchymal tumours

Mixed epithelial and mesenchymal tumours

- Mixed malignant epithelial and mesenchymal tumours
  - Adenosarcoma

Sex cord–stromal tumours

- Pure stromal tumours
  - Ovarian fibroma
  - Thecoma
  - Luteinised thecoma associated with sclerosing peritonitis
  - Sclerosing stromal tumour
  - Microcystic stromal tumour
  - Signet-ring stromal tumour
  - Leydig cell tumour
  - Steroid cell tumour
  - Ovarian fibrosarcoma
- Pure sex cord tumours
  - Adult granulosa cell tumour
  - Juvenile granulosa cell tumour
  - Sertoli cell tumour
  - Sex cord tumour with annular tubules
- Mixed sex cord–stromal tumours
  - Sertoli–Leydig cell tumour
  - Sex cord–stromal tumour, NOS
  - Gynandroblastoma

Germ cell tumours

- Mature teratoma
- Immature teratoma
- Dysgerminoma
- Yolk sac tumour
- Embryonal carcinoma
- Non-gestational choriocarcinoma
- Mixed germ cell tumour
- Monodermal teratomas and somatic-type tumours arising from a dermoid cyst
  - Struma ovarii
  - Ovarian carcinoid
  - Neuroectodermal-type tumours
  - Monodermal cystic teratoma
  - Somatic neoplasms arising from teratomas
- Germ cell–sex cord–stromal tumours
  - Gonadoblastoma
  - Mixed germ cell–sex cord–stromal tumour, unclassified

Miscellaneous tumours

- Rete cystadenoma, adenoma, and adenocarcinoma
- Wolffian tumour
- Solid pseudopapillary tumour
- Small cell carcinoma of the ovary, hypercalcaemic type
- Wilms tumour

Tumour-like lesions

- Follicle cyst
- Corpus luteum cyst
- Large solitary luteinised follicle cyst
- Hyperreactio luteinalis
- Pregnancy luteoma
- Stromal hyperplasia and hyperthecosis
- Fibromatosis and massive oedema
- Leydig cell hyperplasia

Tumours of the peritoneum

Mesothelial tumours

- Adenomatoid tumour
- Well-differentiated papillary mesothelial tumour
- Mesothelioma

Epithelial tumours

- Epithelial tumours of Müllerian type
  - Serous borderline tumour
  - Low-grade serous carcinoma
  - High-grade serous carcinoma

Mesenchymal tumours specific to peritoneum

- Smooth muscle tumours
  - Leiomyomatosis peritonealis disseminata
- Miscellaneous primary tumours
  - Desmoid fibromatosis
  - Calcifying fibrous tumour
  - Extragastrointestinal stromal tumour
  - Solitary fibrous tumour
  - Endometrioid stromal sarcoma
  - Desmoplastic small round cell tumour

Tumour-like lesions

- Mesothelial hyperplasia
- Peritoneal inclusion cysts
- Transitional cell metaplasia
- Endosalpingiosis
- Histiocytic nodule
- Ectopic decidua
- Splenosis
- Other tumour-like lesions

Tumours of the fallopian tube

Epithelial tumours

- Benign serous tumours
  - Serous adenofibroma and papilloma
- Borderline serous tumours
  - Serous borderline tumour
- Malignant epithelial tumours
  - High-grade serous carcinoma
  - Endometrioid carcinoma
  - Carcinosarcoma

Tumour-like lesions

- Paratubal cysts
- Tubal hyperplasia
- Tubo-ovarian abscess
- Salpingitis isthmica nodosa
- Metaplastic papillary lesion
- Placental site nodule
- Mucinous metaplasia
- Endosalpingiosis

Mixed epithelial and mesenchymal tumours

- Adenosarcoma

Germ cell tumours

- Teratoma

Tumours of the broad ligament and other uterine ligaments

Mesenchymal and mixed tumours

- Leiomyoma
- Adenomyoma
- Adenosarcoma
- Leiomyosarcoma
- Other mesenchymal and mixed tumours

Miscellaneous tumours

- Wolffian tumour
- Papillary cystadenoma
- Ependymoma

Tumour-like lesions

- Adrenocortical remnants

Tumours of the uterine corpus

Endometrial epithelial tumours and precursors

- Precursor lesions
  - Endometrial hyperplasia without atypia
  - Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia
- Endometrial carcinomas
  - Endometrioid carcinoma
  - Serous carcinoma
  - Clear cell carcinoma
  - Undifferentiated and dedifferentiated carcinomas
  - Mixed carcinoma
  - Other endometrial carcinomas
  - Carcinosarcoma

Tumour-like lesions

- Endometrial polyp
- Endometrial metaplasia
- Arias-Stella reaction

Mesenchymal tumours of the uterus

- Smooth muscle tumours
  - Uterine leiomyoma
  - Intravenous leiomyomatosis
  - Smooth muscle tumour of uncertain malignant potential
  - Metastasising leiomyoma
  - Uterine leiomyosarcoma
- Endometrial stromal and related tumours
  - Endometrial stromal nodule
  - Low-grade endometrial stromal sarcoma
  - High-grade endometrial stromal sarcoma
  - Undifferentiated uterine sarcoma
- Miscellaneous mesenchymal tumours
  - Uterine tumour resembling ovarian sex cord tumour
  - Perivascular epithelioid cell tumour (PEComa)
  - Inflammatory myofibroblastic tumour
  - Other mesenchymal tumours of the uterus

Mixed epithelial and mesenchymal tumours

- Adenomyoma
- Atypical polypoid adenomyoma
- Adenosarcoma

Miscellaneous tumours

- Central primitive neuroectodermal tumour/CNS embryonal tumour
- Germ cell tumours

Gestational trophoblastic disease

Tumour-like lesions

- Non-neoplastic lesions
  - Exaggerated placental site reaction
  - Placental site nodule and plaque

Abnormal (non-molar) villous lesions

Molar pregnancies

- Partial hydatidiform mole
- Complete hydatidiform mole
- Invasive and metastatic hydatidiform moles

Gestational trophoblastic neoplasms

- Epithelioid trophoblastic tumour
- Placental site trophoblastic tumour
- Gestational choriocarcinoma
- Mixed trophoblastic tumour

Tumours of the uterine cervix

Squamous epithelial tumours

- Mimics of squamous precursor lesions
  - Squamous metaplasia
  - Atrophy
- Squamous cell tumours and precursors
  - Squamous intraepithelial lesions
  - Squamous cell carcinoma, HPV-associated
  - Squamous cell carcinoma, HPV-independent
  - Squamous cell carcinoma, NOS

Glandular tumours and precursors

- Benign glandular lesions
  - Endocervical polyp
  - Müllerian papilloma
  - Nabothian cyst
  - Tunnel clusters
  - Microglandular hyperplasia
  - Lobular endocervical glandular hyperplasia
  - Diffuse laminar endocervical hyperplasia
  - Mesonephric remnants and hyperplasia
  - Arias-Stella reaction
  - Endocervicosis
  - Tuboendometrioid metaplasia
  - Ectopic prostate tissue
- Adenocarcinomas
  - Adenocarcinoma *in situ*, HPV-associated
  - Adenocarcinoma, HPV-associated
  - Adenocarcinoma *in situ*, HPV-independent
  - Adenocarcinoma, HPV-independent, gastric type
  - Adenocarcinoma, HPV-independent, clear cell type
  - Adenocarcinoma, HPV-independent, mesonephric type
  - Other adenocarcinomas

Other epithelial tumours

- Carcinosarcoma
- Adenosquamous and mucoepidermoid carcinomas
- Adenoid basal carcinoma
- Carcinoma, unclassifiable

Mixed epithelial and mesenchymal tumours

- Adenomyoma
- Adenosarcoma

Germ cell tumours

Tumours of the vagina

Epithelial tumours

- Benign squamous lesions
  - Squamous papilloma
  - Tubulosquamous polyp
- Squamous cell tumours and precursors
  - Squamous intraepithelial lesions
  - Squamous cell carcinoma, HPV-associated
  - Squamous cell carcinoma, HPV-independent
  - Squamous cell carcinoma, NOS
- Benign glandular lesions
  - Villous adenoma
  - Müllerian papilloma
  - Vaginal adenosis
  - Endocervicosis
  - Cysts
- Glandular tumours
  - Adenocarcinoma, HPV-associated
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Mucinous carcinoma, gastric type
  - Mucinous carcinoma, intestinal type
  - Mesonephric adenocarcinoma
  - Carcinosarcoma
- Other epithelial tumours
  - Mixed tumour of the vagina
  - Adenocarcinoma of Skene gland origin
  - Adenosquamous carcinoma
  - Adenoid basal carcinoma

Mixed epithelial and mesenchymal tumours

- Adenosarcoma

Miscellaneous tumours

- Germ cell tumours

Tumours of the vulva

Epithelial tumours

- Benign squamous lesions
  - Seborrhoeic keratosis
  - Condyloma acuminatum
- Squamous cell tumours and precursors
  - Squamous intraepithelial lesions, HPV-associated
  - Vulvar intraepithelial neoplasia, HPV-independent
  - Squamous cell carcinoma, HPV-associated
  - Squamous cell carcinoma, HPV-independent
  - Squamous cell carcinoma, NOS
  - Basal cell carcinoma
- Glandular tumours and cysts
  - Mammary-type glandular lesions
    - Papillary hidradenoma
    - Chondroid syringoma
    - Fibroadenoma
    - Phyllodes tumour
    - Adenocarcinoma of mammary gland type
  - Bartholin gland lesions
    - Bartholin gland cyst
    - Hyperplasia, adenoma, and adenomyoma
    - Bartholin gland carcinomas
  - Other cysts
  - Adenocarcinomas of other types
    - Paget disease
    - Carcinomas of sweat gland origin
    - Adenocarcinoma of intestinal type

Germ cell tumours

Neuroendocrine neoplasia

Neuroendocrine tumour

Neuroendocrine carcinoma

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Mixed neuroendocrine–non-neuroendocrine neoplasms

- Carcinoma admixed with neuroendocrine carcinoma

Haematolymphoid proliferations and neoplasia

Reactive lymphoid hyperplasia

- Florid reactive lymphoid hyperplasia

Lymphomas

- Diffuse large B-cell lymphoma
- Extranodal marginal zone lymphoma
- Follicular lymphoma
- Burkitt lymphoma

Myeloid leukaemia

- Myeloid sarcoma

Mesenchymal tumours of the lower genital tract

Adipocytic tumours

- Lipoma
- Lipoblastoma-like tumour of the vulva
- Liposarcoma

Fibroblastic and myofibroblastic tumours

- Postoperative spindle cell nodule
- Fibroepithelial stromal polyp
- Prepubertal fibroma
- Superficial myofibroblastoma
- Myofibroblastoma
- Cellular angiofibroma
- Angiomyofibroblastoma
- Solitary fibrous tumour
- Dermatofibrosarcoma protuberans
- *NTRK*-rearranged spindle cell neoplasm (emerging)

Vascular tumours

- Kaposi sarcoma
- Angiosarcoma

Smooth muscle tumours

- Leiomyoma
- Smooth muscle tumour of uncertain malignant potential
- Leiomyosarcoma

Skeletal muscle tumours

- Rhabdomyoma
- Rhabdomyosarcoma

Peripheral nerve sheath tumours

- Benign peripheral nerve sheath tumours
- Granular cell tumour

Tumours of uncertain differentiation

- Superficial angiomyxoma
- Deep (aggressive) angiomyxoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma

Undifferentiated small round cell sarcomas

- Ewing sarcoma

Melanocytic lesions

Naevi

- Acquired melanocytic naevus
- Congenital melanocytic naevus
- Blue naevus
- Atypical melanocytic naevus of genital type
- Dysplastic melanocytic naevus

Melanoma

- Mucosal melanoma

Abbreviations: CNS, central nervous system; HPV, human papillomavirus; NOS, not otherwise specified; NTRK, neurotrophic tyrosine receptor kinase; WHO, World Health Organization.

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

Appendix 2: FIGO Cancer Staging Systems and Corresponding TNM

Cancer of the ovary, fallopian tube and peritoneum

TNM staging	FIGO staging (2021)	Description
T1 N0 M0	**Stage I**	Tumour confined to ovaries or fallopian tube(s)
T1a N0 M0	Stage 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
T1b N0 M0	Stage 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
	Stage IC	Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following:
T1c1 N0 M0	Stage IC1	Surgical spill
T1c2 N0 M0	Stage IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
T1c3 N0 M0	Stage IC3	Malignant cells in the ascites or peritoneal washings
T2 N0 M0	**Stage II**	Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
T2a N0 M0	Stage IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2b N0 M0	Stage IIB	Extension to other pelvic intraperitoneal tissues
T1-3/N0-1/M0	**Stage III**	Tumour involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
T1/T2 N1 M0	Stage IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
	Stage IIIA1(i)	Metastasis up to 10 mm in greatest dimension
	Stage IIIA1(ii)	Metastasis more than 10 mm in greatest dimension
T3a2 N0/N1 M0	Stage IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b N0/N1 M0	Stage IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3c N0/N1 M0	Stage IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Any T, Any N, M1	**Stage IV**	Distant metastasis excluding peritoneal metastases
	Stage IVA	Pleural effusion with positive cytology
	Stage IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour, node, metastasis.

Cancer of the vulva

TNM staging	FIGO staging (2021)	Description
Tis N0 M0		Carcinoma *in situ* (pre-invasive)
	Stage I	Tumour confined to the vulva or perineum
T1a N0 M0	Stage IA	Tumour size ≤2 cm and stromal invasion ≤1 mm[a]
T1b N0 M0	Stage IB	Tumour size >2 cm or stromal invasion >1 mm[a]
T2 N0 M0	**Stage II**	Tumour of any size with extension to lower 1/3 of the urethra, lower 1/3 of the vagina, lower 1/3 of the anus, with negative nodes
	Stage III	Tumour of any size with extension to upper part of adjacent perineal structures, or with any number of non-fixed, non-ulcerated lymph node
T1/T2 N1a/N1b M0	Stage IIIA	Tumour of any size with disease extension to upper 2/3 of the urethra, upper 2/3 of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
T1/T2 N2a/ N2b M0	Stage IIIB	Regional[b] lymph node metastases >5 mm
T1/T2 N2c M0	Stage IIIC	Regional[b] lymph node metastases with extracapsular spread
	Stage IV	Tumour of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases
T1/T2/T3 N3 M0	Stage IVA	Disease fixed to pelvic bone, or fixed or ulcerated regional[b] lymph node metastases
Any T, Any N, M1	Stage IVB	Distant metastases

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour, node, metastasis.

[a]Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.

[b]Regional refers to inguinal and femoral lymph nodes.

Cancer of the cervix uteri

TNM staging	FIGO staging (2019)	Description
Tis N0 M0		Carcinoma *in situ* (preinvasive carcinoma)
T1 N0 M0	**Stage I**	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
T1a[1] N0 M0	Stage IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm[a]
T1a1 N0 M0	Stage IA1	Measured stromal invasion ≤3 mm in depth
T1a2 N0 M0	Stage IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
T1b N0 M0	Stage IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter[b]
T1b1 N0 M0	Stage IB1	Invasive carcinoma >5 mm depth of stromal invasion, and ≤2 cm in greatest dimension
T1b2 N0 M0	Stage IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
T1b3 N0 M0	Stage IB3	Invasive carcinoma >4 cm in greatest dimension
T2 N0 M0	**Stage II**	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
T2a N0 M0	Stage IIA	Involvement limited to the upper 2/3 of the vagina without parametrial invasion
T2a1 N0 M0	Stage IIA1	Invasive carcinoma ≤4 cm in greatest dimension
T2a2 N0 M0	Stage IIA2	Invasive carcinoma >4 cm in greatest dimension
T2b N0 M0	Stage IIB	With parametrial involvement but not up to the pelvic wall
T3 N0 M0	**Stage III**	The carcinoma involves the lower 1/3 of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
T3a N0 M0	Stage IIIA	The carcinoma involves the lower 1/3 of the vagina, with no extension to the pelvic wall
T3b N0 M0	Stage IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	Stage IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases)[c], irrespective of tumour size and extent (with r and p notations)[d]
TX, T0, Tis, T1, T2, T3 N1 M0	Stage IIIC1	Pelvic lymph node metastasis only
TX, T0, Tis, T1, T2, T3 N2 M0	Stage IIIC2	Para-aortic lymph node metastasis
	Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
T4 Any N M0	Stage IVA	Carcinoma has involved (biopsy-proven) the mucosa of the bladder or rectum or has spread to adjacent organs
Any T, Any N, M1	Stage IVB	Spread to distant organs

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; TNM, tumour, node, metastasis.

[1]Vascular space involvement, venous or lymphatic, does not affect classification.

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings.

[b]The involvement of vascular/lymphatic spaces does not change staging. The lateral extent of the lesion is no longer considered.

[c]Isolated tumour cells do not change the stage but their presence should be recorded.

[d]Adding notation of r (imaging) and p (pathology), to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r; if confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

Cancer of the endometrium

TNM staging	FIGO staging (2023)	Description
Tis N0 M0		Carcinoma *in situ* (preinvasive carcinoma)
T1 N0 M0	**Stage I**	Confined to the uterine corpus and ovary[a]
T1a N0 M0	Stage IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease
	Stage IA1	Non-aggressive[b] histological type limited to an endometrial polyp OR confined to the endometrium
	Stage IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	Stage IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
T1b N0 M0	Stage IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
	Stage IC	Aggressive[c] histological types limited to a polyp or confined to the endometrium
T2 N0 M0	**Stage II**	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
	Stage IIA	Invasion of the cervical stroma of non-aggressive histological types
	Stage IIB	Substantial LVSI[d] of non-aggressive histological types
	Stage IIC	Aggressive histological types with any myometrial involvement
T3 N0 M0	**Stage III**	Local and/or regional spread of the tumour of any histological subtype
T3a N0 M0	Stage IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	Stage IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c]
	Stage IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
T3b N0 M0	Stage IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	Stage IIIB1	Metastasis or direct spread to the vagina and/or the parametria
	Stage IIIB2	Metastasis to the pelvic peritoneum
	Stage IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
T1-T3 N1/ N1mi/N1a M0	Stage IIIC1	Metastasis to the pelvic lymph nodes
	Stage IIIC1i	Micrometastasis
	Stage IIIC1ii	Macrometastasis
T1-T3 N2/ N2mi/N2a M0	Stage IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	Stage IIIC2i	Micrometastasis[e]
	Stage IIIC2ii	Macrometastasis[e]
	Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis
T4 Any N M0	Stage IVA	Invasion of the bladder mucosa and/or the intestinal/ bowel mucosa
Any T, Any N, M1	Stage IVB	Abdominal peritoneal metastasis beyond the pelvis
	Stage IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain or bone

[a]Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI;
(3) absence of additional metastases; and (4) the ovarian tumour is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

[b]Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6%–50%); and high grade (possibly aggressive[c]) = grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumour by one. The presence of unusual nuclear atypia in an architecturally low-grade tumour should prompt the evaluation of p53 and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component.

[c]Aggressive histological types are composed of most, but not all, high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas. It should be noted that high-grade EECs (grade 3) are a prognostically, clinically and molecularly heterogenous disease, and the tumour type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making. Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.

[d]LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

[e]According to TNM8, macrometastases are >2 mm in size, micrometastases are 0.2–2 mm and/or >200 cells, and ITCs are ≥0.2 mm and ≤200 cells. Micrometastases are considered to be metastatic involvement (pN1 (mi)). The prognostic significance of ITCs is unclear. The presence of ITCs should be documented and is regarded as pN0(i+).

Abbreviations: EEC, endometrioid endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumour cell; LVSI, lymphovascular space invasion; TNM, tumour, node, metastasis; WHO World Health Organization.

FIGO molecular classification

Where feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLE*mut, dMMR, NSMP, p53-abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

- Good prognosis: pathogenic *POLE*mut
- Intermediate prognosis: dMMR/microsatellite instability and NSMP
- Poor prognosis: p53-abn
- When the molecular classification is known:
  - FIGO stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLE*mut or p53-abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLE*mut or p53-abn status, as shown below. dMMR or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals dMMR or NSMP, it should be recorded as stage Im_{MMRd} or stage Im_{NSMP} and stage IIm_{MMRd} or stage IIm_{NSMP}.
  - FIGO stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as stage IIIm or stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53-abn, it should be recorded as stage $IIIm_{p53\text{-}abn}$ or stage $IVm_{p53\text{-}abn}$.

Stage designation	Molecular findings in patients with early endometrial cancer (stages I and II after surgical staging)
Stage $IAm_{POLE\,mut}$	*POLE*mut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53\text{-}abn}$	p53-abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Abbreviations: dMMR, mismatch repair deficient; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, POLE ultramutated.

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G. Aletti: No conflict of interest.

A. Berner: Personal invited speaker honoraria: Servier for non-promotional talk on cancer genomics, Pfizer Oncology for non-promotional event in cancer genomics, Eisai for non-promotional video on genomics, Pfizer for internal talk on LGBTQ+ cancer care, Lilly for internal talk on LGBTQ+ cancer care, Astellas for non-promotional talk on LGBTQ+ cancer care; personal advisory board honoraria: Pfizer; travel grant: Gilead; institutional funding: Gilead.

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L. Dostalek: No conflict of interest.

C. Fotopoulou: Personal invited speaker honoraria: Roche, AstraZeneca, MSD, Sequana, GSK, Ethicon; personal advisory board honoraria: Oncoinvent.

A. González-Martín: Personal advisory board honoraria: Alkermes, Amgen, AstraZeneca, Clovis Oncology, Eisai, GSK, Genmab, HederaDx, Illumina, ImmunoGen, MacroGenics, Mersana Therapeutics, MSD, Novartis, Oncoinvent, PharmaMar, Regeneron, Roche, Seagen, Sotio Biotech, Sutro Biopharma, Tubulis; personal invited speaker honoraria: AstraZeneca, Clovis Oncology, MSD, Novocure, Roche, Seagen, Takeda, Zai Lab; personal steering committee member honoraria: MSD; institutional funding for his work as coordinating principal investigator: Aravive, GSK, Novartis, Roche.

M.J. Halaska: Personal advisory honoraria: SOTIO.

M. Hall: Personal advisory board honoraria: Amgen, AstraZeneca, Clovis Oncology, GSK; personal speaker honoraria: Clovis Oncology, GSK; institutional research grants: Bristol Myers Squibb (BMS), Clovis Oncology (CeNtuRIOn clinical trial – Glasgow Clinical Trials Unit), Merck (CoRinTh clinical trial – Cardiff Clinical Trials Unit).

S. Howlett: No conflict of interest.

A. Leary: Personal advisory board honoraria: Zentalis; personal invited speaker honoraria: GSK, Medscape; personal writing honoraria: Onko+; personal consultancy honoraria: GLG; institutional advisory board honoraria: GSK, AstraZeneca, Clovis Oncology, Ability Pharma, MSD, Merck Serono, Apmonia, Blueprint; institutional steering committee honoraria: MSD; institutional invited speaker honoraria: Kephren Publishing, AstraZeneca, Clovis Oncology; institutional consultancy honoraria: Orion, Owkin; institutional steering committee honoraria: MSD; institutional research grants: ARCAGY-GINECO, Sanofi, AstraZeneca, OSE Immuno; institutional funding: Agenus, Roche, BMS, AstraZeneca, Iovance, MSD, GSK. She has non-remunerated roles as an independent data monitoring committee chair for Pfizer and is involved in academic research projects with Owkin and LXRepair.

S. Mahner: Personal advisory board honoraria: AbbVie, AstraZeneca, Clovis Oncology, Eisai, Novartis, Seagen; personal invited speaker honoraria: Hubro Therapeutics, GSK, MSD, Nykode, Pfizer, Roche, Tesaro; institutional research grants: AstraZeneca, Eisai, GSK, MSD, Roche, Tesaro.

S. Marnitz: No conflict of interest.

C. Marth: Personal advisory board honoraria: AstraZeneca, Roche Austria, Novartis, MSD, PharmaMar, GSK, Pfizer, ImmunoGen, Daiichi Sankyo, BioNTech, Novocure, Eisai; personal invited speaker honoraria: AstraZeneca, Roche, GSK, Novartis, MSD, PharmaMar, Roche; his institution has received research grants from AstraZeneca, Roche.

K. Prieske: No conflict of interest.

S. Quesada: No conflict of interest.

I. Ray-Coquard: Personal advisory board honoraria: Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis Oncology, Daiichi Sankyo, Deciphera, EQRx, Eisai, GSK, ImmunoGen, MacroGenics, Merck Serono, Mersana Therapeutics, Novartis, Oxnea, PMV Pharma, Roche, Seagen, Sutro; institutional funding for her role in translational research trials: BMS (COLIBRI trial), MSD (NeoPembrOV trial). She has been a principal investigator for the PAOLA-1 study; President of the GINECO group.

L. Rob: No conflict of interest.

L. Sánchez-Lorenzo: Invited speaker honoraria: AstraZeneca, GSK; travel grants: AstraZeneca, GSK, Pfizer, Roche.

C. Sessa: Personal data monitoring committee honoraria: Merck; personal honoraria: advisor for genealogical cancers for ESO (European School of Oncology). She holds non-remunerated advisory roles as a member of the ESMO Compliance Committee and as an extended member of the ESMO Women for Oncology Committee.

B. Slomovitz: Personal advisory board honoraria: Aadi, AstraZeneca, Clovis Oncology, Eisai, GSK, Genentech, Incyte, Merck, Immunogen, Novocure, Regeneron, Seagen; personal consultancy honoraria: GOG Foundation. He holds a non-remunerated role as a member of the Board of Directors of the GOG Foundation.

J. Villamayor: No conflict of interest.

V. Wieser: No conflict of interest.

L. Woelber: Personal advisory board honoraria: AstraZeneca, Eisai, GSK, MSD, Roche, Seagen; personal invited speaker honoraria: AstraZeneca, Med Publico GmbH, MSD, Novartis, Pfizer, Roche, Seagen; personal scientific board honoraria: Med Update GmbH; institutional funding for her work as coordinating principal investigator: Medac Pharma, Seagen; funding for her work as local principal investigator: MSD, Roche, Nykode; institution product samples: Roche Diagnostics. She is the current President of the European College for the Study of Vulval Disease (ECSVD); she has leadership roles in the AGO Study Group and AGO Commission Vulva Vagina.

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