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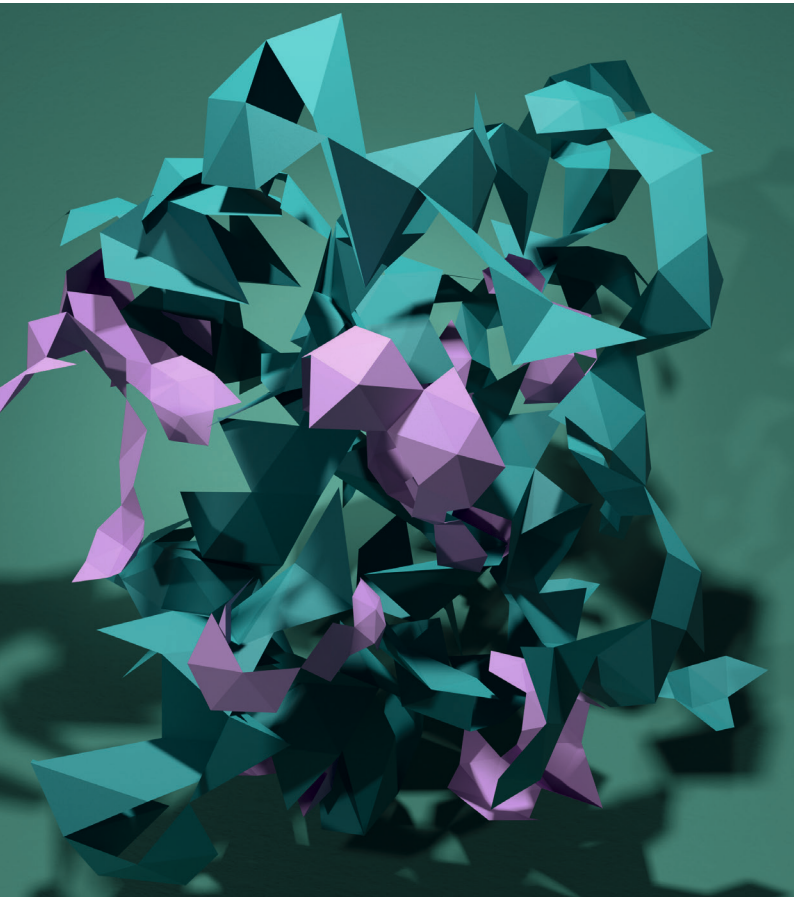
Gynaecological Cancers

Pocket Guideline 2023



ESMO POCKET GUIDELINES

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ESMO CLINICAL PRACTICE GUIDELINES

Cervical cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A and Colombo N, on behalf of the ESMO Guidelines Committee
Ann Oncol 2017;28(Suppl 4):iv72-83
https://www.annalsofoncology.org/article/S0923-7534(19)42148-0/fulltext

Gestational trophoblastic disease: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L and Sessa C, on behalf of the ESMO Guidelines Working Group
Ann Oncol 2013;24(Suppl 6):vi39-50
https://www.annalsofoncology.org/article/S0923-7534(19)31565-0/fulltext

Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, Lorusso D, Marth C, Makker V, Mirza MR, Ledermann JA and Colombo N, on behalf of the ESMO Guidelines Committee
Ann Oncol 2022;33(9):860-77
https://www.annalsofoncology.org/article/S0923-7534(22)01207-8/fulltext

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ESMO POCKET GUIDELINES (CONT'D)

Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline
Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, Domchek SM, Evans DG, Fischerova D, Harbeck N, Kuhl C, Lemley B, Levy-Lahad E, Lambertini M, Ledermann JA, Loibl S, Phillips K-A and Paluch-Shimon S, on behalf of the ESMO Guidelines Committee
Ann Oncol 2023;34(1):33-47
https://www.annalsofoncology.org/article/S0923-7534(22)04193-X/fulltext

Non-epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
Ray-Coquard I, Morice P, Lorusso D, Prat J, Oaknin A, Pautier P and Colombo N, on behalf of the ESMO Guidelines Committee
Ann Oncol 2018;29(Suppl 4):iv1-18
https://www.annalsofoncology.org/article/S0923-7534(19)31689-8/fulltext

Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, Ray-Coquard I, Tan DSP, Bellet E, Oaknin A and Ledermann JA, on behalf of the ESMO Guidelines Committee
Ann Oncol 2023; in press
https://www.annalsofoncology.org/article/S0923-7534(23)00797-4/fulltext

ESMO GUIDE TO EVALUATION OF DATA

ESMO POCKET GUIDELINES PROVIDE YOU WITH A CONCISE SUMMARY OF THE FUNDAMENTAL RECOMMENDATIONS MADE IN THE PARENT GUIDELINES IN AN EASILY ACCESSIBLE FORMAT.

This quick reference booklet provides you with the most important content of the ESMO Clinical Practice Guidelines (CPGs) on the management of gynaecological cancers (including cervical cancer, gestational trophoblastic disease, endometrial cancer, hereditary ovarian cancer syndromes, non-epithelial ovarian cancer and epithelial ovarian cancer). Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up. The ESMO CPGs on gynaecological cancers are intended to provide you with a set of recommendations for the best standards of care for gynaecological cancers, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

The approval and licensed indication of drugs mentioned in this pocket guideline may vary in different countries. Please consult your local prescribing information. This booklet can be used as a quick reference guide to access key content on evidence-based management of gynaecological cancers.

Please visit http://www.esmo.org or http://oncologypro.esmo.org to view the full guidelines.

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CERVICAL CANCER

DIAGNOSIS

- Abnormal cervical cytology or a positive high-risk human papillomavirus (HPV) test should lead to colposcopy and biopsy or excisional procedures such as loop electrosurgical excision and conisation
- Early cervical cancer is often asymptomatic, while symptoms of locally advanced disease include abnormal vaginal bleeding (also after coitus), discharge, pelvic pain and dyspareunia
- Gross appearance is variable, with carcinomas being exophytic or endophytic, and both early and deeply invasive tumours may be difficult to detect on gross examination
- Where examination is difficult, or vaginal/parametrial involvement is uncertain, the examination should be conducted under anaesthesia by an interdisciplinary team including a gynaecological oncologist and a radiation oncologist
- The three World Health Organization (WHO) categories of cervical epithelial tumours are: Squamous (~70-80%), glandular [adenocarcinoma (AC); 20-25%] and other [including adenosquamous carcinoma (ASC), neuroendocrine tumours (NETs) and undifferentiated carcinoma], as shown in the table on the next page

Squamous cell carcinoma

- Squamous cell carcinomas (SCCs) can be classified as keratinising, non-keratinising and small cell
  - The WHO classification reserves the term small cell carcinoma for tumours of neuroendocrine type
- Keratinising SCCs have keratin pearls whereas non-keratinising SCCs may show only individual cell keratinisation
- Clear cell changes prominent in some tumours should not be misinterpreted as clear cell carcinoma

ACs

- Most (80%) ACs are endocervical or usual; tumour cells are not obviously mucinous and have eosinophilic cytoplasm
- The most common type is the mucinous type, comprising endocervical, intestinal and gastric subtypes
- Mucin-rich cells predominate in mucinous AC
- Mixed ASCs (including glassy cell carcinoma) are rare and other ACs, including clear cell carcinoma, are even rarer

WHO HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE UTERINE CERVIX

CATEGORY
Epithelial tumours
Squamous tumours and precursors
SCC, NOS - Keratinising - Non-keratinising - Basaloid - Verrucous - Warty - Papillary - Lymphoepithelioma-like - Squamotransitional
Early invasive (microinvasive) SCC
Squamous intraepithelial neoplasia - CIN 3/SCC *in situ*
Benign squamous cell lesions - Condyloma acuminatum - Squamous papilloma - Fibroepithelial polyp
Glandular tumours and precursors
AC - Mucinous AC - Endocervical - Intestinal - Signet-ring cell - Minimal deviation - Villoglandular - Endometrioid AC - Clear cell AC - Serous AC - Mesonephric AC
Early invasive AC
AC *in situ*
Glandular dysplasia
Benign glandular lesions - Müllerian papilloma - Endocervical polyp
Other epithelial tumours
ASC - Glassy cell carcinoma variant
Adenoid cystic carcinoma
Adenoid basal carcinoma
NETs - Carcinoid - Atypical carcinoid - Small cell carcinoma - Large cell neuroendocrine carcinoma
Undifferentiated carcinoma
Mesenchymal tumours and tumour-like conditions
Mixed epithelial and mesenchymal tumours
Melanocytic tumours
Miscellaneous tumours
Lymphoid and haematopoietic tumours
Secondary tumours

AC, adenocarcinoma; ASC, adenosquamous carcinoma; CIN, cervical intraepithelial neoplasia; NET, neuroendocrine tumour; NOS, not otherwise specified; SCC, squamous cell carcinoma; WHO, World Health Organization

Other cervical carcinomas

- NETs include carcinoids, atypical carcinoids and neuroendocrine carcinomas
- Diagnosis is histological and can be confirmed with neuroendocrine markers

Pathogenesis and molecular biology

- HPV is the most important aetiological factor in cervical cancer, with HPV 16/18 accounting for at least two-thirds of cervical carcinomas
- Almost all SCCs and their precursor, intraepithelial squamous lesions, are HPV infection-related, and HPV 16 DNA is associated with poor prognosis
- ACs are heterogeneous, with most endocervical ACs of usual type and their precursor, AC *in situ*, being HPV-positive, but with rarer types, including clear cell and mesonephric AC, appearing to be unrelated to HPV
- HPV 18 is more common in ACs and ASCs than in SCCs

STAGING AND RISK ASSESSMENT

- Cervical tumours are staged using the International Federation of Gynecology and Obstetrics (FIGO) and the Union for International Cancer Control (UICC) tumour–node–metastasis (TNM) eighth edition staging classifications, as shown in the table below

STAGING OF CERVICAL CANCER ACCORDING TO FIGO AND THE UICC TNM EIGHTH EDITION

TNM CATEGORY	FIGO STAGE	DEFINITION
Primary tumour (T)		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma *in situ* (preinvasive carcinoma)
T1	I	Tumour confined to the cervix*
T1a[†,‡]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of ≤ 7.0 mm[§]
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread of ≤ 7.0 mm[§]
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion > T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T1b2	IB2	Carcinoma *in situ* (preinvasive carcinoma)
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[‖]
Regional lymph nodes (N)[¶]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)[¶]		
M0		No distant metastasis
M1		Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa and adnexa

*Extension to corpus uteri should be disregarded

†The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification

‡All macroscopically visible lesions, even with superficial invasion, are T1b/IB

§Vascular space involvement, venous or lymphatic, does not affect classification

‖Bullous oedema is not sufficient to classify a tumour as T4

¶No FIGO equivalent

FIGO, International Federation of Gynecology and Obstetrics; M, metastasis; N, node; T, tumour; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control

Brierley JD et al (eds). TNM classification of malignant tumours, Eighth edition: John Wiley & Sons, Inc., Oxford, 2016. Reprinted with permission from John Wiley & Sons, Inc

- Clinical staging is based on tumour size, vaginal or parametrial involvement, bladder/rectum extension and distant metastases, and requires radiological imaging, examination under anaesthesia and intravenous (IV) pyelogram
- Computed tomography (CT) can detect pathological lymph nodes, and magnetic resonance imaging (MRI) can determine tumour size, degree of stromal penetrations, parametrial involvement, vaginal extension and corpus extension with high accuracy

- Positron emission tomography (PET) can accurately delineate the extent of disease with high sensitivity and specificity
- PET-CT is sensitive and specific for the detection of lymph node involvement in early-stage disease and para-aortic node involvement in more advanced stages, although the need for this in locally advanced cervical cancer (LACC) is still under debate
- Tumour risk assessment includes tumour size, stage, depth of tumour invasion, lymph node status, lymphovascular space invasion (LVSI) and histological subtype
  - Lymph node status and number of lymph nodes involved are the most important prognostic factors
- Cervical small cell neuroendocrine carcinoma displays frequent distant spread and patients can present with systemic symptoms or paraneoplastic syndromes

MANAGEMENT OF LOCAL/LOCOREGIONAL CERVICAL CANCER

- Treatment recommendations for cervical cancer are shown in the figure on pages 18 and 19

Primary treatment

Surgery

- Surgical therapy should be adapted to the FIGO/TNM stage of disease
- Microinvasive cervical cancer (stage IA1) without LVSI can be managed with conisation or simple trachelectomy, to preserve fertility, or with simple hysterectomy if fertility preservation is not important to the patient
- In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes, including the sentinel lymph node (SLN), should be discussed with the patient
- In FIGO stage IA2, IB and IIA, radical hysterectomy with bilateral lymph node dissection (with or without SLN) is standard when preservation of fertility is not important to the patient
  - Radical hysterectomy performed by laparoscopy or robot-assisted surgery cannot be regarded as the preferred treatment in comparison with open surgery in patients with FIGO stage IA2, IB and IIA. Patients should be counselled about the risks and benefits of the different types of surgery

SLN dissection in cervical cancer

- SLN dissection (SLND) should be considered in FIGO stage I patients with tumours of ≤ 4 cm; the detection rate may be highest for tumours of < 2 cm
- Tracer, such as blue dye, technetium radiocolloid or fluorescent indocyanine green, is injected directly into the cervix
- Sentinel nodes should be detected on both sides

Surgical therapy of the uterus

- Surgery should only be considered for patients with earlier disease stages (up to FIGO IIA) without risk factors necessitating adjuvant therapy
- Radical hysterectomy with extensive parametrial resection is probably overtreatment for many patients, particularly those with small, locally restricted tumours

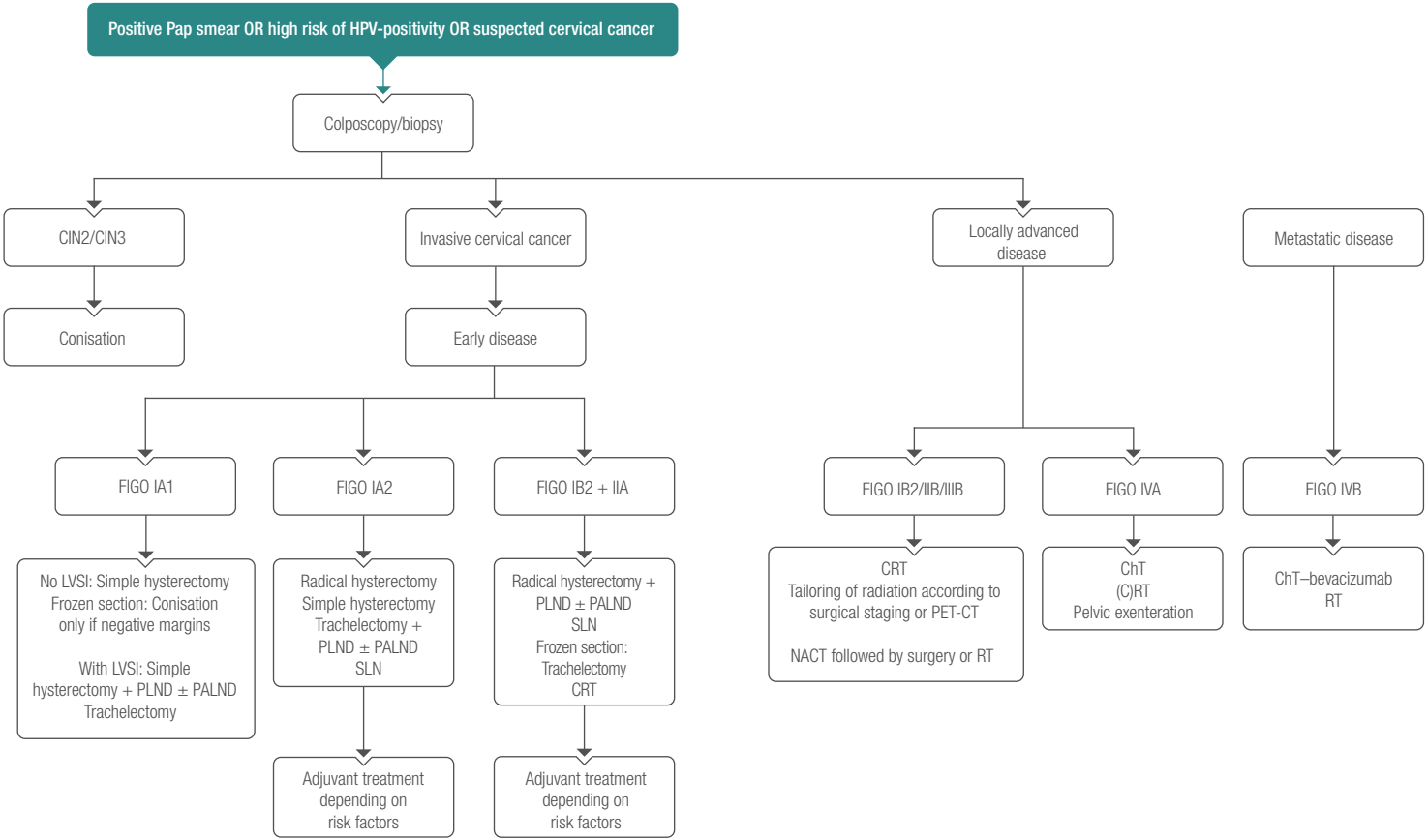
Neoadjuvant chemotherapy prior to surgery

- Neoadjuvant chemotherapy (NACT) followed by radical surgery reduces the risk of death compared with radiotherapy (RT) alone, with an absolute improvement in survival of 14% at 5 years
- However, trials are hampered by the fact that RT without concomitant chemotherapy (ChT) is not the current standard of care (SoC) and by suboptimal RT duration and dose
- NACT followed by surgery provides better local control (odds ratio 0.67) than surgery alone, indicating that it may offer a benefit over surgery by reducing the need for adjuvant RT, although this approach may be limited by toxicity or insufficient response to NACT

Chemoradiotherapy in LACC

- Chemoradiotherapy (CRT) is the SoC for patients with bulky stage IB2-IVA disease, with randomised trials demonstrating an improvement in both disease-free survival (DFS) and overall survival (OS) compared with standard RT–hydroxyurea
- CRT also shows absolute OS and DFS improvements, the survival benefit being greater for patients with FIGO stage I/II compared with FIGO stage III/IVA disease
- The most commonly used regimen is weekly cisplatin 40 mg/m^2, although significant benefits with non-platinum agents have also been reported
- Toxicity concerns limit the wider adoption of a more intensive concomitant approach with gemcitabine–cisplatin-based CRT followed by an additional 2 cycles of adjuvant ChT, despite an improvement in progression-free survival (PFS) compared with cisplatin-based CRT
- High local control rates in FIGO stage IIB and IIIB disease are achieved with brachytherapy, with a low risk of grade 3-5 bladder, gastrointestinal (GI) tract and vaginal morbidity
  - Survival benefits compared with standard CRT with lower RT doses remain to be clarified
- Options for small cell neuroendocrine carcinoma include: Surgery followed by ChT or CRT for limited stage, potentially resectable disease; definitive CRT for locoregionally advanced unresectable but non-metastatic disease; and palliative ChT for metastatic disease with regimens typically used for standard small cell lung cancer

MANAGEMENT OF CERVICAL CANCER



ChT, chemotherapy; CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; PALND, para-aortic lymph node dissection; Pap, Papanicolaou; PET, positron emission tomography; PLND, pelvic lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node

NACT and RT

- Results with neoadjuvant or induction ChT prior to RT are conflicting
- ChT cycle length and platinum dose intensity influence 5-year survival following NACT, with short cycles (≤ 14 days) giving a 7% improvement and longer cycles (> 14 days) an 8% detriment
- The ongoing INTERLACE trial is comparing standard CRT alone with 6 weeks of dose-dense, taxane-based induction ChT followed immediately by standard CRT

Lymph node staging and RT

- For patients with LACC, pelvic MRI and clinical examination is essential to determine the local extent of the tumour for both external beam RT (EBRT) and brachytherapy planning
- Information on para-aortic nodal status is also essential for treatment planning
- The best way to assess the para-aortic nodes, from routine PET-CT to surgical exploration, is being addressed in ongoing randomised trials

Adjuvant treatment

- Women with risk factors on the pathology specimen, defined by the parameters shown in the table below, should receive adjuvant therapy following hysterectomy

NECESSARY HISTOPATHOLOGICAL PARAMETERS FOR ASSESSMENT OF CERVICAL CANCER

HISTOPATHOLOGICAL EVALUATION
Dimensions of the tumour
Stromal invasion/depth of the wall involved
Tumour differentiation
LVSI
Status of resection margins
Status of parametria and vaginal cuff
Number and status of lymph nodes

LVSI, lymphovascular space invasion

Intermediate-risk disease

- Intermediate-risk disease is characterised by the presence of the following risk factors: Tumour size > 4 cm, deep stromal invasion and/or LVSI. Patients with intermediate-risk disease generally do not need further adjuvant therapy
- A significant PFS, but not OS, benefit has been seen with postoperative RT in women with deep cervical stromal invasion (to the middle or one-third depth), LVSI and large tumour size (> 4 cm)

High-risk disease

- High-risk disease is characterised by the presence of one or more negative prognostic factors, such as positive or close surgical margins, positive lymph nodes or microscopic parametrial involvement. Adjuvant CRT is recommended for patients with high-risk disease
- Adjuvant CRT is associated with better OS and PFS than adjuvant RT for patients with stage IA2, IB and IIA disease, particularly for those completing 3-4 cycles of cisplatin–5-fluorouracil

MANAGEMENT OF ADVANCED/METASTATIC CERVICAL CANCER

- Palliative ChT with the aim of relieving symptoms and improving quality of life (QoL) is indicated if the patient has a performance status (PS) ≤ 2 and no formal contraindications
- Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS, with lower responses being associated with previous exposure to CRT, black race, pelvic location, PS 1 or 2 and first relapse within one year of diagnosis
- Cisplatin–paclitaxel is the preferred cisplatin-based doublet (compared with cisplatin–topotecan, –gemcitabine or –vinorelbine) based on the balance between efficacy and toxicity profiles
- In recurrent cervical cancer, adding bevacizumab to ChT significantly prolongs median OS and a non-platinum doublet is not superior to platinum–paclitaxel, even for patients previously treated with cisplatin
  - Side-effects, including hypertension, venous thromboembolic events and fistula, were more common with bevacizumab and should be carefully monitored
- A paclitaxel–carboplatin combination is an alternative for patients who are not candidates for cisplatin
- Paclitaxel–cisplatin–bevacizumab is the preferred first-line regimen in metastatic or recurrent cervical cancer, based on the balance between efficacy and toxicity profile

- For patients progressing following first-line therapy, responses to ChT are few and of short duration (as shown in the table below); as such, no recommendation about the most effective second-line treatment can be given

SECOND-LINE THERAPY FOR METASTATIC CERVICAL CANCER

AGENT	N	CR + PR, %	PFS, MONTHS	OS, MONTHS
Bevacizumab	46	11	3.4	7.3
Topotecan	94	13-19	2.1-2.4	6.4-6.6
Vinorelbine	44	14	–	–
Gemcitabine	22	5	2.1	6.5
Albumin-bound paclitaxel	35	29	5.0	9.4
Docetaxel	23	9	3.8	7.0
Pemetrexed	72	14-15	2.5-3.1	7.4-8.8
Irinotecan	42	21	4.5	6.4
Sunitinib	19	0	3.5	–
Erlotinib	28	0	1.9	5.0
Lapatinib	78	5	4.2	9.7
Pazopanib	74	9	4.5	12.7
Pegylated liposomal doxorubicin	27	11	3.2	8.9

CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response

- High-dose RT can give long-term disease control in recurrent disease, oligometastatic disease and pelvic, periaortic and/or supraclavicular nodal metastases
- Short-course palliative RT can treat distant metastases-related symptoms

Local recurrence of cervical cancer following radical surgery

- Radical RT or pelvic exenteration are options for patients with pelvic relapse following primary surgery, and favourable prognostic factors include disease-free interval, central versus side wall recurrence and size
- Higher RT doses can be delivered with brachytherapy and increase the likelihood of local control for patients with small-volume central recurrences

Fertility preservation

- > 40% of women with early cervical cancer are affected during reproductive age and more conservative management approaches should increase the chances of a future successful pregnancy

FIGO stage IA1

- The first diagnostic and curative step for microscopic tumours is conisation, which, with negative margins and the absence of clinical contraindications to surgery, may represent definitive treatment
- Pelvic lymph node dissection (PLND) is recommended for patients with LVSI and an increased risk of lymph node involvement; sentinel node biopsy can be considered
  - Some authors favour trachelectomy for these patients

FIGO stage IA2

- Cone biopsy or radical trachelectomy with PLND is the standard procedure; sentinel node biopsy can be considered

FIGO stage IB1 < 2 cm

- Trachelectomy with pelvic lymphadenectomy is recommended for tumours measuring ≤ 2 cm in diameter
- Radical trachelectomy is a standard fertility-sparing procedure for early cervical cancer and tumours < 2 cm, but the low incidence of parametrial involvement and lack of nodal disease or LVSI suggests that less radical treatment may also be a valid choice
- As 60-65% of trachelectomy specimens have no residual disease, the need for radical surgery for patients with low-risk tumours is questionable
- Conisation with or without NACT can be considered

FIGO stage IB > 2 cm

- For tumours > 2 cm, NACT followed by conisation or trachelectomy is recommended
- Downstaging by NACT in stage IB2 cervical cancer before fertility-sparing surgery is still experimental

PERSONALISED MEDICINE

- More research is needed to identify molecular markers that could lead to advances in personalised medicine

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- No definitive agreement exists on the best post-treatment surveillance

- At a minimum, follow-up visits with a complete physical examination, including a pelvic-rectal examination and patient history, should be conducted by a physician experienced in the surveillance of cancer patients
- Vaginal vault cytology does not add significantly to the clinical examination in detecting early disease recurrence
- Routine use of various other radiological or biological follow-up investigations in asymptomatic patients is not advocated
- A CT or PET-CT scan should be carried out as clinically indicated
- A reasonable follow-up schedule involves visits every 3-6 months in the first 2 years and every 6-12 months in years 3-5
- Return to annual population-based general physical and pelvic examinations is recommended after 5 years of recurrence-free follow-up

GESTATIONAL TROPHOBLASTIC DISEASE

DIAGNOSIS

- Complete hydatidiform moles (CHMs) and partial hydatidiform moles [PHMs; the premalignant forms of gestational trophoblastic disease (GTD)] most commonly present with vaginal bleeding in the first trimester of pregnancy
- Ultrasound (US) sonography is not diagnostically reliable in the first trimester and histological examination is essential to achieve a correct diagnosis
  - The safest method of evacuation is suction dilation and curettage (D&C) under US control to ensure adequate emptying of uterine contents and to avoid uterine perforation
- Characteristic findings for CHM in the second trimester include a heterogeneous mass ("snowstorm") without foetal development and with theca lutein ovarian cysts
- A proportion of women who miscarry or who undergo medical termination of pregnancy will have unsuspected molar pregnancies
  - Histological examination of every termination is impractical; measurement of urine or serum human chorionic gonadotropin (hCG) 3-4 weeks post-treatment may be indicated
- All women with a diagnosis of molar pregnancy require careful hCG monitoring for recurrence of disease suggesting malignant change indicated by a plateaued or rising hCG on three and two consecutive samples, respectively
  - Re-biopsy to confirm malignant change is not advised because of the risk of triggering life-threatening haemorrhage
- The other malignant forms of GTD, choriocarcinoma (CC) and placental site trophoblastic tumour (PSTT)/epithelioid trophoblastic tumour [ETT; collectively known as gestational trophoblastic tumours or neoplasia (GTN)] can be more challenging to diagnose as the disease can develop months or many years after a prior pregnancy with protean presentations possible
  - It is essential to measure hCG in any woman of childbearing age with unexplained metastatic disease
  - Biopsy without the ability to control bleeding is highly risky in this very vascular disease and is not essential prior to commencing chemotherapy (ChT)
  - Where complete excision is possible, this can provide useful histological confirmation of the diagnosis and material for genetic analysis

STAGING

Indications for treatment

- Following suction curettage of a PHM, patients should have anti-Rhesus D prophylaxis
- After any hydatidiform mole (HM), the onset of malignant change is nearly always indicated by a plateaued or rising hCG
  - The precise hCG surveillance protocol varies by country but principles are similar. In the United Kingdom (UK), serum and urine hCG are measured every 2 weeks until normal levels are reached, then urine hCG is measured monthly
- UK indications for commencing ChT are listed in the table below. These are broadly similar to those of the International Federation of Gynecology and Obstetrics (FIGO)

INDICATIONS FOR CHT FOLLOWING A DIAGNOSIS OF GTD (UK)

• Plateaued or rising hCG after evacuation*
• Heavy vaginal bleeding or evidence of GI or intraperitoneal haemorrhage
• Histological evidence of CC
• Evidence of metastases in brain, liver or GI tract, or radiological opacities > 2 cm on chest X-ray
• Serum hCG ≥ 20,000 IU/L > 4 weeks after evacuation (because of the risk of uterine perforation)

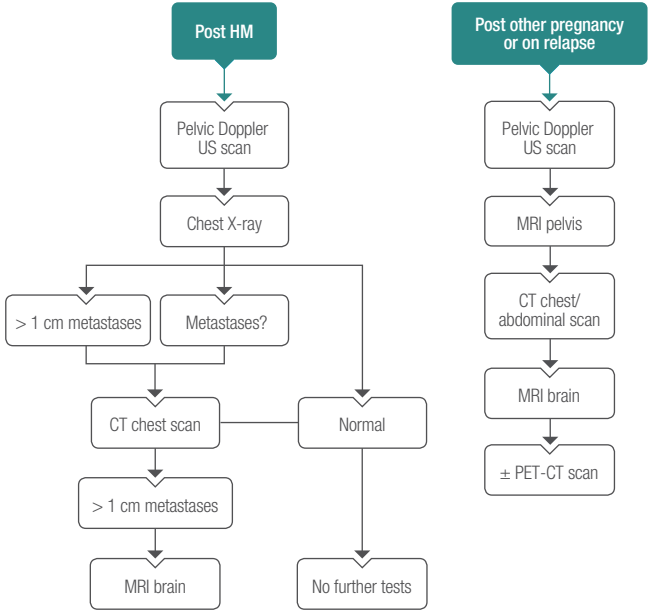
*Plateaued or rising is defined as ≥ 4 equivalent values of hCG over ≥ 3 weeks (days 1, 7, 14 and 21) and two consecutive rises in hCG of ≥ 10% over ≥ 2 weeks (days 1, 7 and 14), respectively

CC, choriocarcinoma; ChT, chemotherapy; GI, gastrointestinal; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; UK, United Kingdom

Staging investigations and treatment stratification after a molar pregnancy

- Most patients developing GTN post-HM are detected early via hCG monitoring so extensive investigation is rarely required
- Information to determine therapy can be obtained from the clinical history, examination, measurement of serum hCG and a Doppler pelvic US to:
  - Confirm the absence of pregnancy
  - Measure the uterine size/volume and spread of disease within the pelvis
  - Assess uterine vascularity
- Imaging investigations in GTN are summarised in the figure on the next page

IMAGING INVESTIGATIONS FOR PATIENTS WITH GTN FOLLOWING A HM ON HCG SURVEILLANCE OR AFTER ANY OTHER TYPE OF PREGNANCY



CT, computed tomography; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; HM, hydatidiform mole; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound

- Pulmonary metastases are common so chest X-ray is essential; computed tomography (CT) scan of the chest is not required if the chest X-ray findings are normal
  - If lesions are noted on chest X-ray, magnetic resonance imaging (MRI) of the brain and CT scan of the body are indicated
- FIGO staging for GTN is as follows:
  - Stage I: Disease confined to the uterus
  - Stage II: Disease extending into the pelvis
  - Stage III: Disease spread to lungs and/or vagina
  - Stage IV: All other metastatic sites including liver, kidney, spleen and brain

- FIGO prognostic scoring for GTN is shown in the table below. The prognostic score predicts the potential for developing resistance to single-drug ChT with methotrexate or actinomycin D; a high risk of resistance requires multi-agent treatment

FIGO PROGNOSTIC SCORING SYSTEM FOR GTN (2000)

PROGNOSTIC FACTOR	SCORE			
	0	1	2	4
Age (years)	< 40	≥ 40	-	-
AP	Mole	Abortion	Full term	-
Interval (end of AP to ChT in months)	< 4	4-6	7-12	> 12
hCG (IU/L)	$< 10^3$	10^3-10^4	10^4-10^5	$> 10^5$
Number of metastases	0	1-4	5-8	> 8
Sites of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest tumour mass	-	3-5 cm	> 5 cm	-
Prior ChT	-	-	Single drug	≥ 2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Low risk: 0-6; high risk: ≥ 7. PSTT should not be scored and instead requires staging

AP, antecedent pregnancy; ChT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; GI, gastrointestinal; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; PSTT, placental site trophoblastic tumour

Staging investigations for choriocarcinoma and placental site trophoblastic tumour/ epithelioid trophoblastic tumour

- Staging for women who present with an elevated hCG and suspected GTN following a prior pregnancy require contrast-enhanced CT of the chest and abdomen, MRI of the brain and pelvis and Doppler US of the pelvis
  - They may also benefit from a lumbar puncture to assess the cerebrospinal fluid to serum hCG ratio; a ratio of > 1:60 suggests occult central nervous system (CNS) disease
  - Where there is doubt over the clinical diagnosis, tissue should be obtained and genetic analysis undertaken to confirm the gestational origin of the tumour through the presence of paternal genes
- For CC, the FIGO scoring/staging system is the same as described above
- For PSTT/ETT, this system is not valid but FIGO staging is used to help adapt treatment intensity

- Positron emission tomography (PET)-CT imaging is not widely used but may be helpful in relapsed disease to identify sites for resection

TREATMENT

Management of low-risk gestational trophoblastic neoplasia

- For nearly all patients with low-risk (FIGO score < 7) GTN, single-agent ChT with either methotrexate or actinomycin D is the preferred treatment
  - The most commonly used methotrexate dosing regimen is 50 mg by intramuscular injection every 48 hours for a total of 4 doses, with calcium folinate (folinic acid) 15 mg orally 30 hours after each injection of methotrexate, repeated every 2 weeks
  - A large, international randomised study is currently evaluating the optimal regimen for both methotrexate and actinomycin D
- Patients failing first-line therapy can be easily salvaged with second- and occasionally third-line ChT so that overall survival (OS) is ~100%; as such, the least toxic therapy should be selected first
  - The methotrexate–folinic acid regimen may be preferred over actinomycin D as it does not induce hair loss and, after a short stay in hospital to monitor for bleeding complications, most patients can be treated at home by their general practitioner or in their nearest hospital
- hCG should ideally be measured at least once per week during ChT until normal levels are reached and then for a further 6 weeks
- Patients with a FIGO risk score of 5-6 may require first-line multi-agent therapy as only ~30% can expect a cure with single-agent ChT
  - Efforts are now underway to identify factors that might enable identification of the 70% of patients who develop methotrexate–folinic acid resistance; these may include the vascularity seen on Doppler US and an hCG > 400,000 IU/L

Management of high-risk gestational trophoblastic neoplasia

- Multi-agent ChT is recommended for patients with high-risk (FIGO score ≥ 7) GTN
- Suitable ChT regimens include: Methotrexate–folinic acid–actinomycin D (MFA), actinomycin D–cyclophosphamide–doxorubicin–melphalan–hydroxyurea–vincristine (CHAMOCA), methotrexate–actinomycin D–cyclophosphamide (MAC), etoposide–methotrexate–actinomycin D and others
- A regimen developed at Charing Cross Hospital (London, UK) is widely accepted and consists of etoposide–methotrexate–actinomycin D alternating weekly with cyclophosphamide–vincristine (CO) (see table on the next page)
  - Granulocyte colony-stimulating factor (G-CSF) may be required for some patients

ETOPOSIDE–METHOTREXATE–ACTINOMYCIN D/CO CHT REGIMEN FOR PATIENTS WITH HIGH-RISK GTN

DAY	REGIMEN	SCHEDULE
Etoposide–methotrexate–actinomycin D		
Day 1	Etoposide Actinomycin D Methotrexate	100 mg/m^2 by IV infusion over 30 mins 0.5 mg IV bolus 300 mg/m^2 by IV infusion over 12 hours
Day 2	Etoposide	100 mg/m^2 by IV infusion over 30 mins
	Actinomycin D	0.5 mg IV bolus
	Folinic acid rescue (starting 24 hours after commencing the methotrexate infusion)	15 mg IV or orally every 12 hours for 4 doses
CO		
Day 8	Vincristine Cyclophosphamide	1 mg/m^2 IV bolus (maximum 2 mg) 600 mg/m^2 IV infusion over 30 mins

Etoposide–methotrexate–actinomycin D alternates with CO every week. To avoid extended intervals between courses caused by myelosuppression, it may occasionally be necessary to reduce the intensity of the etoposide–methotrexate–actinomycin D regimen by omitting the day 2 doses of etoposide and actinomycin D

ChT, chemotherapy; CO, cyclophosphamide–vincristine; GTN, gestational trophoblastic neoplasia; IV, intravenous

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- To reduce the risk of death for patients with very advanced disease, commencing ChT gently with low-dose etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2 repeated for 1-3 weeks may be helpful
  - This approach can be combined with genetic testing to exclude non-gestational CC
- ChT should be continued for 6 weeks of normal hCG values or 8 weeks if poor prognostic features, such as liver or brain metastases, are present
  - Imaging should then be repeated to document the post-treatment appearance for future comparison
  - Removal of residual masses is unnecessary as it does not reduce the risk of recurrence

Management of drug-resistant gestational trophoblastic neoplasia

- hCG monitoring facilitates the detection of early relapse and drug resistance
- In relapsed patients:
  - [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-PET scanning may help identify the site of active disease to facilitate surgical resection and cure
  - If surgical resection is not possible or the hCG falls inappropriately, several salvage regimens are available including etoposide–cisplatin (EP) alternating weekly with etoposide–methotrexate–actinomycin D (omitting the second day of etoposide and actinomycin D)

- Drug-resistant GTN has been reported to respond and/or be cured by paclitaxel-based single-agent or combination therapy, gemcitabine and capecitabine
- An alternating two-weekly doublet of paclitaxel–cisplatin (TP) and paclitaxel–etoposide (TE) may be better tolerated than EP/etoposide–methotrexate–actinomycin D and is effective for patients with relapsed and/or refractory disease (see table below)

TP/TE CHT REGIMEN FOR RELAPSED AND/OR REFRACTORY GTN

REGIMEN	SCHEDULE
Day 1	
Dexamethasone	20 mg oral (12 hours pre-paclitaxel)
Dexamethasone	20 mg oral (6 hours pre-paclitaxel)
Cimetidine	20 mg in 100 mL normal saline over 30 mins IV
Chlorphenamine	10 mg bolus IV
Paclitaxel	135 mg/m^2 250 mL normal saline over 3 hours IV
Mannitol	10% in 500 mL over 1 hour IV
Cisplatin	60 mg/m^2 1 L normal saline over 3 hours IV
Post-hydration	1 L normal saline + potassium chloride 20 mMol + 1 g magnesium sulphate over 2 hours IV
Day 15	
Dexamethasone	20 mg oral (12 hours pre-paclitaxel)
Dexamethasone	20 mg oral (6 hours pre-paclitaxel)
Cimetidine	30 mg in 100 mL normal saline over 30 mins IV
Chlorphenamine	10 mg bolus IV
Paclitaxel	135 mg/m^2 in 250 mL normal saline over 3 hours IV
Etoposide	150 mg/m^2 in 1 L normal saline over 1 hour IV

ChT, chemotherapy; GTN, gestational trophoblastic neoplasia; IV, intravenous; TE, paclitaxel–etoposide; TP, paclitaxel–cisplatin

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- An alternative for patients with refractory disease involves high-dose ChT (HDCT) with peripheral stem cell transplantation, although cures are not common and improved patient selection may be required to improve outcomes with this approach

Management of placental site trophoblastic tumour and epithelioid trophoblastic tumour

- Patients with metastatic disease require combination ChT, e.g. with EP/etoposide–methotrexate–actinomycin D continued for 8 weeks of normal hCG levels
- Residual masses should be removed surgically together with the uterus since this can harbour microscopic disease
  - Hysterectomy with pelvic lymph node sampling and ovarian conservation is preferred unless there is a family history of ovarian cancer or the patient is postmenopausal
- In the absence of sufficient data regarding adjuvant therapy, 8 weeks of EP/etoposide–methotrexate–actinomycin D or TE/TP is advocated when there are poor risk factors such as disease presenting beyond 4 years of the antecedent pregnancy; HDCT could be considered for these patients
  - Careful counselling of younger patients regarding the risk of fertility-sparing surgery in this setting should be undertaken

PERSONALISED MEDICINE

- Traditionally, targeted agents have not been used in the management of GTN due to the sensitivity of these tumours to ChT and the early detection of resistance due to serial hCG measurements
- In the very rare cases of multidrug resistant disease not amenable to surgical resection, vascular targeting agents such as bevacizumab might be active
- As GTN tumours can overexpress the epidermal growth factor receptor (EGFR), anti-EGFR agents such as erlotinib or gefitinib might also be active
- However, the efficacy of these targeted agents has yet to be demonstrated in clinical trials
- The potential for an anti-hCG targeted therapy has not been explored and could be of interest in women who have completed their families or in those where no alternative therapies remain

FOLLOW-UP

- Careful hCG monitoring is required and pregnancy should ideally be delayed for at least the first year of follow-up
  - In the UK, hCG is monitored weekly for 6 weeks after ChT, then in serum and urine every other week until 6 months. Monthly urine testing is then continued, eventually decreasing to 6-monthly, and should be continued lifelong (see the table on the next page)

FOLLOW-UP PROTOCOL OF PATIENTS WITH GTN AFTER CHT (UK)

YEAR	TIMING	HCG CONCENTRATION SAMPLING	
		URINE	BLOOD
1	Week 1-6 after ChT	Weekly	Weekly
	Months 2-6	Every 2 weeks	Every 2 weeks
	Months 7-12	Every 2 weeks	-
2		Every 4 weeks	-
3		Every 8 weeks	-
4		Every 3 months	-
5		Every 4 months	-
> 5		Every 6 months	-

ChT, chemotherapy; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; UK, United Kingdom

- When a patient becomes pregnant, it is important to confirm by US and other appropriate means that the pregnancy is normal. Follow-up is then discontinued but the hCG should be checked again at 6 and 10 weeks after the pregnancy to ensure no recurrence or new disease
- Long-term monitoring of treated patients is advocated, especially for those who received combination ChT for > 6 months who may face an increased risk for second tumours

ENDOMETRIAL CANCER

DIAGNOSIS

- Most (80%) endometrial cancers (ECs) are diagnosed while confined to the uterus and present with post-menopausal bleeding
- Obtaining endometrial sampling by biopsy or dilation and curettage are acceptable initial approaches to histological diagnosis of EC
  - Hysteroscopy may be helpful to have a representative biopsy or for removal of the target lesion

Pathology and molecular biology

- Tumours are graded according to the International Federation of Gynecology and Obstetrics (FIGO) criteria and are moving towards a two-tier grading: Low grade (grade 1 and 2 tumours) and high grade (grade 3 tumours)
- Factors traditionally identified as high risk for recurrent disease include: Grade 3 tumours, histological subtype, myometrial invasion ≥ 50%, lymph node metastases and tumour diameter > 2 cm
- Major poor prognostic factors include: L1 cell adhesion molecule [most frequently expressed in tumour protein p53 (p53)-abnormal (p53-abn) tumours] and substantial lymphovascular space invasion (LVSI; widespread invasion of tumour emboli into vascular spaces at and beyond the invasive front of the tumour)
  - LVSI can be diagnosed on haematoxylin and eosin slides without need for additional immunostains, with substantial LVSI defined as ≥ 4 LVSI-positive vessels in at least one slide
- EC classification is undergoing a transition period from histological to molecular classification; thus, it is important to specify the system used
  - ECs that have not been (completely) molecularly classified should be designated as "not otherwise specified" and continue the use of the histology-based classification system
- Histopathological classification of EC comprises Type 1 (endometrioid subtype) and Type 2 (all other subtypes, including carcinosarcoma; generally associated with higher risk of relapse)
  - The histology-based classification distinguishes endometrioid EC (EEC), serous, clear cell and un/dedifferentiated EC
- A molecular classification system proposed by The Cancer Genome Atlas (TCGA) project stratifies ECs into four distinct molecular groups:
  - Ultramutated [> 100 mutations/megabase (mut/Mb)] with pathogenic variations in the exonuclease domain of DNA polymerase epsilon *(POLE)*-ultramutated (*POLE*mut)
  - Hypermutated (10-100 mut/Mb), microsatellite-unstable
  - Somatic copy number alteration-high (SCNA-high) with frequent pathogenic variants in tumour suppressor protein p53 *(TP53)*
  - SCNA-low with frequent phosphoinositide 3-kinase and WNT signalling abnormalities
- This pragmatic alternative relies on a small number of well-established immunohistochemistry (IHC) markers [MutS homologue 6 (MSH6), PMS1 homologue 2 (PMS2) and p53] in combination with targeted tumour sequencing (*POLE* hotspot analysis), without the need for extensive sequencing, as shown in the table on the next page
  - This approach automatically pre-screens for Lynch syndrome as it incorporates reflex testing of the mismatch repair (MMR) proteins
- Molecular classification should be carried out for all EC pathology specimens regardless of histological type, as shown in the algorithm on page 37
  - This should include well-established IHC staining for p53 and MMR proteins [MutL homologue 1 (MLH1), PMS2, MutS homologue 2 (MSH2), MSH6] in combination with targeted tumour sequencing (*POLE* hotspot analysis)
  - Where laboratory limitations are present, molecular classification should be prioritised for cases where results may guide adjuvant treatment recommendations, particularly for those classified as high grade or stage (FIGO stage ≥ II)

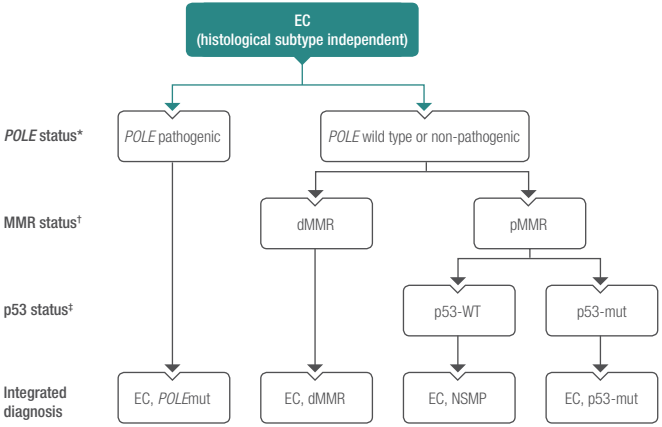
MOLECULAR AND CLINICOPATHOLOGICAL FEATURES OF EC MOLECULAR SUBGROUPS

	***POLE*mut** (i.e. *POLE* EDM)	**dMMR** (i.e. MSI-H)	**NSMP** (i.e. p53-WT)	**p53 ABERRANT** (i.e. p53-abn, p53-mut)
Prevalence in TCGA cohort	5-15%	25-30%	30-40%	5-15%
Associated molecular features	> 100 mut/Mb, SCNA-very low, MSS	10-100 mut/Mb, SCNA-low, MSI-H	< 10 mut/Mb, SCNA-low, MSS	< 10 mut/Mb, SCNA-high, MSS
Most frequently associated histological features	Endometrioid Often high grade Ambiguous morphology Prominent TILs and TLSs	Endometrioid Often high grade LVSI substantial Prominent TILs MELF-type invasion	Mostly low grade Notable absence of TILs Squamous differentiation ER/PgR diffuse	All histological subtypes Mostly high grade High cytonuclear atypia Low level of TILs
Associated clinical features	Lower BMI Early stage (IA-IB) Early onset	Higher BMI Lynch syndrome	Higher BMI	Lower BMI Advanced stage Late onset
Diagnostic test	NGS/Sanger/ Hotspot: P286R, V411L, S297F, A456P, S459F	MMR-IHC: MLH1, MSH2, MSH6, PMS2 MSI assay		p53-IHC Mutant-like/ abnormal staining
Prognosis	Excellent	Intermediate	Intermediate Stage-dependent	Poor

BMI, body mass index; dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain mutation; ER, oestrogen receptor; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented type of invasion; MLH1, MutL homologue 1; MMR, mismatch repair; MSH2, MutS homologue 2; MSH6, MutS homologue 6; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; mut/Mb, mutations per megabase; NGS, next-generation sequencing; NSMP, no specific molecular profile; p53-abn, p53-abnormal; p53-mut, p53-mutated; p53-WT, p53-wild type; PgR, progesterone receptor; PMS2, PMS1 homologue 2; *POLE*, polymerase epsilon; *POLE*mut, polymerase epsilon-ultramutated; SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas; TIL, tumour infiltrating lymphocyte; TLS, tertiary lymphoid structure

McAlpine J et al. J Pathol 2018;244(5):538-49. Adapted with permission from John Wiley and Sons

DIAGNOSTIC ALGORITHM FOR THE INTEGRATED MOLECULAR EC CLASSIFICATION



This algorithm can be applied to all histological subtypes of EC, including carcinosarcomas

*Pathogenic *POLE* variants include p.Pro286Arg, p.Val411Leu, p.Ser297Phe, p.Ala456Pro and p.Ser459Phe

†MMR deficiency is defined by loss of one or more MMR proteins (MLH1, PMS2, MSH2 and MSH6)

‡p53-IHC is an acceptable surrogate marker for *TP53* mutation status in pMMR, *POLE* wild type EC

dMMR, mismatch repair deficient; EC, endometrial cancer; IHC, immunohistochemistry; MLH1, MutL homologue 1; MMR, mismatch repair; MSH2, MutS homologue 2; MSH6, MutS homologue 6; NSMP, no specific molecular profile; p53, tumour protein p53; p53-mut, p53-mutated; p53-WT, p53-wild type; pMMR, mismatch repair proficient; PMS2, PMS1 homologue 2; *POLE*, polymerase epsilon; *POLE*mut, polymerase epsilon-ultramutated; *TP53*, tumour suppressor protein p53

Vermij L et al. Histopathol 2020;76(1):52-63. Permission to use figure under a Creative Commons CC BY License, Wiley https://www.creativecommons.org/licenses/by-nc-nd/2.0/

STAGING AND RISK ASSESSMENT

- EC is surgically staged according to the FIGO system, as shown in the table on the next page
  - However, preoperative staging may help to establish a recurrence risk group and to define resulting surgical management, mainly based on myometrial/cervical invasion and lymph node metastases
- The preoperative work-up should include: Clinical and gynaecological examination, transvaginal ultrasound, pelvic magnetic resonance imaging (MRI), a complete blood count and liver and renal function profiles
- An abdominal and thoracic computed tomography (CT) scan should be considered for investigating the presence of extrapelvic disease

STAGING OF EC (FIGO 2009)

STAGE	CHARACTERISTICS
I	Tumour confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumour invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Tumour invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics
Pecorelli S. Int J Gynaecol Obstet 2009;105(2):103-4. Reprinted with permission from John Wiley and Sons

- [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT demonstrates high specificity and positive predictive value for detecting distant metastases

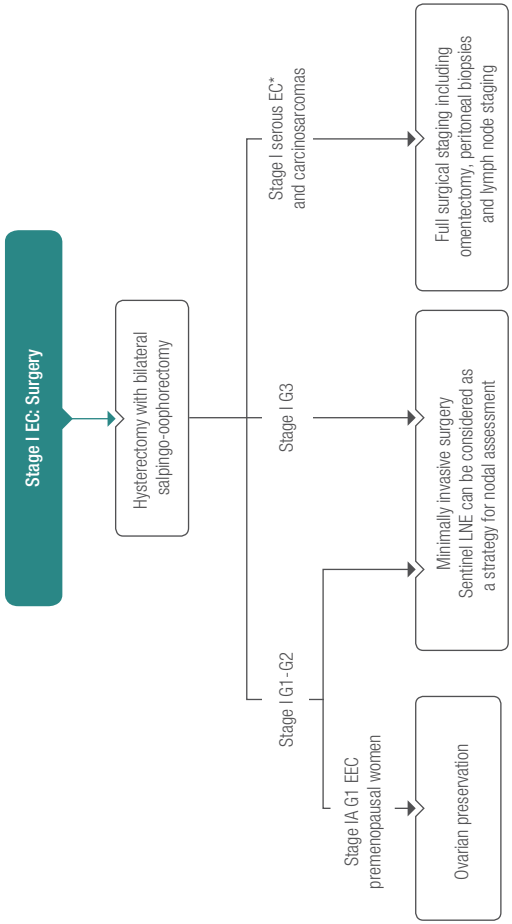
TREATMENT

Management of local and locoregional endometrial cancer

Surgery

- In early-stage EC, the aim of surgery is to remove macroscopic tumour, examine for microscopic metastases and stage the tumour to assess the need for adjuvant therapy, as shown in the figure on the opposite page
- Hysterectomy with bilateral salpingo-oophorectomy is the standard surgical procedure in early-stage EC

STAGE I EC: SURGERY



*Except in those restricted to polyps
EC, endometrial cancer; EEC, endometrioid EC; G, grade; LNE, lymphadenectomy

- Minimally invasive surgery has similar prognostic outcomes as laparotomy and is the recommended approach in stage I, grade 1-2 EC
  - It may also be the preferred surgical approach in stage I, grade 3 EC as no detrimental effects have been demonstrated
- Ovarian preservation can be considered in premenopausal patients with stage IA, grade 1 EEC but is not recommended for patients at genetic risk for ovarian cancer (e.g. germline *BRCA* mutation, Lynch syndrome)
- Full surgical staging, including omentectomy, peritoneal biopsies and lymph node staging, should be considered in serous ECs and carcinosarcomas
- Maximal cytoreductive surgery should be considered in stage III and IV EC (including carcinosarcoma), where feasible and with acceptable morbidity

Lymphadenectomy in the surgical management of early-stage EC

- Sentinel lymphadenectomy (LNE) can be considered for lymph node staging in low- or intermediate-risk EC (e.g. stage IA, grade1-3 and stage IB, grade 1-2)
  - It can be omitted in cases without myometrial invasion
  - Systematic LNE is not recommended
- Sentinel lymph node biopsy may also represent an acceptable alternative to systematic LNE for lymph node staging in high–intermediate- and high-risk, stage I-II disease

Adjuvant therapy for low-, intermediate-, high–intermediate- and high-risk EC

- Molecular classification, which improves the evaluation of recurrence risk, has been integrated with well-established clinicopathological data to provide an updated risk classification system, as shown in the table below

EC RISK GROUPS

RISK GROUP	DESCRIPTION*
Low risk	Stage IA (G1-2) with endometrioid type (dMMR† and NSMP) and no or focal LVSI
	Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers‡
Intermediate risk	Stage IA, G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI
	Stage IA non-endometrioid type (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI
	Stage IB (G1-2) with endometrioid type (dMMR and NSMP) and no or focal LVSI
	Stage II, G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) and any grade and any depth of invasion with substantial LVSI
	Stage IB, G3 with endometrioid type (dMMR and NSMP) regardless of LVSI
	Stage II, G1 endometrioid type (dMMR and NSMP) with substantial LVSI
	Stage II, G2-3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion
	All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion
	All Stage III and IVA with no residual tumour, regardless of histology and molecular subtype†

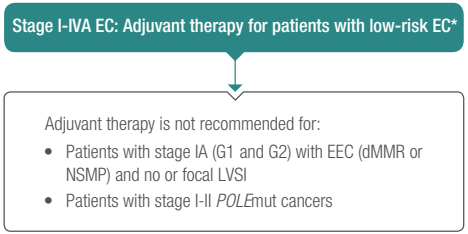
*Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV

†dMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determine microsatellite instability (i.e. MSI-H)

‡*POLE*mut stage III might be considered as low risk. Nevertheless, currently there is no data regarding the safety of omitting adjuvant therapy

EC, endometrial cancer; dMMR, mismatch repair deficient; G, grade; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability-high; NSMP, no specific molecular profile; p53, tumour protein p53; p53-abn, p53-abnormal; *POLE*mut, polymerase epsilon-ultramutated

ADJUVANT TREATMENT OF LOW-RISK EC



*If completely resected without residual disease

dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid EC; G, grade; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; *POLE*mut, polymerase epsilon-ultramutated

- The need for adjuvant treatment is based on the relative risk of disease recurrence; all recommendations apply to women with FIGO stage I-IVA EC who undergo surgery and do not have any macroscopic residual disease

Low-risk EC

- Adjuvant treatment for patients with low-risk EC is shown in the figure on the previous page
- Adjuvant treatment is not recommended for patients with stage IA (grades 1 and 2) endometrioid type [mismatch repair deficient (dMMR) and no specific molecular profile (NSMP)] and no or focal LVSI, stage IA non-endometrioid type (and/or p53-abn) without myometrial invasion and no or focal LVSI, and stage I-II *POLE*mut cancers
- Omitting adjuvant treatment is also an option for stage III *POLE*mut patients; clinical studies (observational) are strongly encouraged in this patient group

Intermediate-risk EC

- Adjuvant treatment for patients with intermediate-risk EC is shown in the figure below

ADJUVANT TREATMENT OF INTERMEDIATE-RISK EC

Stage I-IVA EC: Adjuvant therapy for patients with intermediate-risk EC*

For patients with stage IA G3 EEC (dMMR or NSMP) and no or focal LVSI
- Adjuvant VBT is recommended
- Omission of adjuvant brachytherapy can be considered, especially for patients < 60 years

For patients with stage IB G1-G2 EEC (dMMR or NSMP) and no or focal LVSI
- Adjuvant VBT is recommended
- Omission of adjuvant brachytherapy can be considered, especially for patients < 60 years

For patients with Stage II G1 EEC (dMMR or NSMP) and no or focal LVSI
- Adjuvant VBT is recommended
- Omission of adjuvant brachytherapy can be considered, especially for patients < 60 years

For patients with Stage IA p53-abn tumours not infiltrating the myometrium or restricted to a polyp
- Adjuvant therapy is not recommended

*If completely resected without residual disease

dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid EC; G, grade; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53, tumour protein p53; p53-abn, p53-abnormal; VBT, vaginal brachytherapy

- Adjuvant vaginal brachytherapy (VBT) to decrease vaginal recurrence is recommended in patients with stage IA, grade 3; stage IB, grade 1-2; or stage II, grade 1 endometrioid type (dMMR and NSMP) and no or focal LVSI
  - Omission of adjuvant VBT can be considered (especially for patients aged < 60 years) for all of the above stages after patient counselling and with appropriate follow-up

- No adjuvant treatment is recommended for patients with stage IA, p53-abn tumours not infiltrating the myometrium or restricted to a polyp

High–intermediate-risk EC

- The traditional high–intermediate-risk group has been redefined due to increased knowledge regarding molecular and clinicopathological characteristics, and comprises a group with higher risk of recurrence
- Adjuvant treatment for patients with high–intermediate-risk EC is shown in the figure below

ADJUVANT TREATMENT OF HIGH–INTERMEDIATE-RISK EC

Stage I-IVA EC: Adjuvant therapy for patients with high–intermediate-risk EC*

High–intermediate risk, pN0 after lymph node staging

High–intermediate risk, without lymph node staging

For patients with stage IA and IB with substantial LVSI

For patients with stage IB G3

For patients with stage II G1 with substantial LVSI

For patients with stage II G2-G3 (dMMR or NSMP)
- Adjuvant EBRT is recommended
- Adding (concomitant and/or sequential) ChT to EBRT could be considered, especially for G3 and/or substantial LVSI

*If completely resected without residual disease

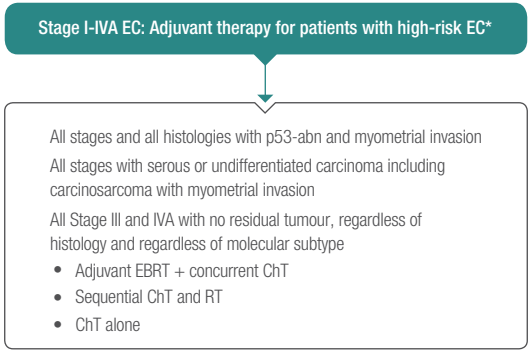
ChT, chemotherapy; dMMR, mismatch repair deficient; EBRT, external-beam radiotherapy; EC, endometrial cancer; G, grade; LVSI, lymphovascular space invasion; N, node; NSMP, no specific molecular profile; p, pathological

- Adjuvant external-beam radiotherapy (EBRT) is recommended for patients with node-negative disease or no lymph node staging and tumour stage IA or IB with substantial LVSI; stage IB, grade 3; stage II, grade 1 with substantial LVSI; or stage II, grade 2-3 EC (dMMR and NSMP)
  - Adding (concomitant and/or sequential) chemotherapy (ChT) to EBRT can be considered, especially for grade 3 tumours and/or substantial LVSI
  - Adjuvant VBT (instead of EBRT) may be recommended to decrease vaginal recurrence, especially for those without substantial LVSI
  - Provided there is close follow-up, omission of any adjuvant treatment is an option following shared decision making with the patient

High-risk EC

- Adjuvant treatment for patients with high-risk EC is shown in the figure below

ADJUVANT TREATMENT OF HIGH-RISK EC



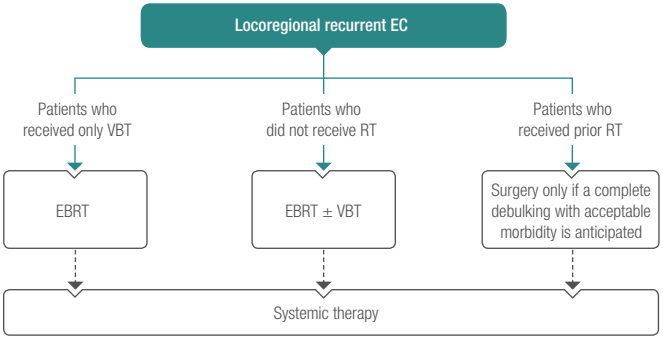
*If completely resected without residual disease
ChT, chemotherapy; EBRT, external-beam radiotherapy; EC, endometrial cancer; p53, tumour protein p53; p53-abn, p53-abnormal; RT, radiotherapy

- Adjuvant EBRT with concurrent and adjuvant ChT is recommended
- Sequential ChT and RT can be used
- ChT alone is an alternative option
- RT alone may be recommended in cases of major comorbidities and contraindications to ChT

Management of recurrent/metastatic endometrial cancer

- Outcomes for patients with advanced/recurrent disease remain poor and treatment should always comprise a multidisciplinary approach in specialised centres
  - Treatment should be guided by the patient's condition, extent of the disease, prior therapies and molecular profile
- Treatment options for patients with EC and locoregional recurrence is shown in the figure opposite
- RT with VBT is the preferred primary therapy for patients with locoregional recurrence following primary surgery alone
  - Adding systemic therapy to salvage RT can be considered

LOCOREGIONAL RECURRENT EC



The dashed lines indicate optional treatments
EBRT, external-beam radiotherapy; EC, endometrial cancer; RT radiotherapy; VBT, vaginal brachytherapy

- For patients with recurrent disease following RT, surgery should only be considered if a complete debulking with acceptable morbidity is anticipated
  - Complementary systemic therapy after surgery can be considered
- Surgery may also be an option for patients with oligometastatic disease (defined as 1-5 metastatic tumours)
- For patients with relapsed disease not amenable to surgery and/or RT, the standard approach remains ChT or hormonal therapy, as shown in the figure on the next page
  - The standard first-line ChT in this setting is carboplatin area under the curve (AUC) 5-6 plus paclitaxel 175 mg/m^2 every 21 days for six cycles
  - Hormone therapy can be considered for patients with low-grade carcinomas and endometrioid histology
    - The recommended agents are progestins (medroxyprogesterone acetate 200 mg and megestrol acetate 160 mg)
    - Other options include aromatase inhibitors, tamoxifen and fulvestrant
- There is no standard of care second-line ChT; doxorubicin and weekly paclitaxel are considered the most active therapies
- Platinum-based ChT rechallenge may be considered an option for selected patients who relapse > 6 months after their last platinum-based ChT

RECURRENT/METASTATIC EC

*In patients eligible for further treatment after failure of platinum-based ChT
†FDA approval is restricted to patients whose tumours are not MSI-H or dMMR
AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; dMMR, mismatch repair deficient; EC, endometrial cancer; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient

- Immune checkpoint inhibitor monotherapy can be considered after platinum-based therapy failure in patients with microsatellite instability-high (MSI-H)/dMMR EC
  - Dostarlimab and pembrolizumab are approved as monotherapy by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for this indication
  - Pembrolizumab is also FDA approved (not EMA approved) for the treatment of tumour mutation burden-high solid tumours (as determined by the FoundationOne CDx assay) that have progressed following prior therapy for EC
  - Pembrolizumab–lenvatinib is approved by the EMA for all patients with EC who have failed a previous platinum-based ChT and who are not candidates for curative surgery or radiotherapy (FDA approval is restricted to patients with EC whose tumours are not dMMR/MSI-H)

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- For patients with low-risk EC, the suggested follow-up (comprising physical and gynaecological examination) is every 6 months for the first 2 years and then yearly until 5 years
  - Follow-up by telephone can be an alternative for patients in this group
- For patients in the high-risk groups, physical and gynaecological examination are recommended every 3 months for the first 3 years, and then every 6 months until 5 years
  - A CT or PET-CT could be considered in this group, particularly if node extension was present
- Patient education regarding the signs and symptoms of recurrence is a critical component of post-treatment care
- The main long-term symptoms reported by EC survivors are fatigue, psychosocial distress, sexuality and gynaeco-urinary disorders, chronic pain, lymphoedema and neuropathy (if ChT was given)
  - Regular exercise, a healthy diet and weight management should be promoted
  - Psycho-educational programmes may improve mood disorders and sexuality complaints

HEREDITARY OVARIAN CANCER SYNDROMES

INCIDENCE AND EPIDEMIOLOGY

- Hereditary breast and ovarian cancer syndrome (HBOC) is defined:
  - Clinically by family history criteria
  - Molecularly by identification of germline pathogenic variants (PVs) in clinically-validated HBOC genes
- HBOC genes are broadly classified as:
  - High-risk genes, which increase cancer risk by at least fourfold
  - Moderate-risk genes, which increase cancer risk by two- to fourfold
- Lifetime cancer risks for HBOC-associated PVs are shown in the table opposite
- Individuals with a significant family history should be offered genetic testing using multigene panels of clinically-validated HBOC genes
- The genetic basis of around half of clinical HBOCs is currently unknown or unexplained by single-gene variants
- Conversely, approximately half of individuals who harbour PVs in HBOC genes do not have a suggestive family history
  - Clinicians should be aware that family history-based testing misses about half of HBOC gene carriers
  - Strategies to identify these high-risk individuals are being developed
- Germline PVs are identified in ~15% of patients with high-grade ovarian cancer
- The prevalence of molecular HBOC in unaffected individuals varies based on family history and ethnicity
  - Some populations harbour founder PVs with high carrier frequencies (e.g. 1:40 for *BRCA1* and *BRCA2* PVs in Ashkenazi Jews)
  - Studies performed in non-founder populations suggest that the carrier frequency for high-risk genes [i.e. *BRCA1*, *BRCA2*, partner and localiser of *BRCA2 (PALB2)*] is approximately 1:150

POST-TEST COUNSELLING AND FOLLOW-UP OF INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Genetic counselling

- Post-test genetic counselling should include discussion of the medical and psychological implications for the individual and their family
  - Medical implications include the impact on treatment of any current cancer and interventions for prevention or early detection of future cancers

LIFETIME CANCER RISKS IN HBOC-ASSOCIATED PVS

	BC*	TUBO-OVARIAN CANCERS†	PANCREATIC CANCER‡	COLON CANCER§	OTHER CANCERS
ATM	Yes 25-30%	Yes < 5%	Yes < 5%	No	Prostate: 30%
BARD1	Yes ~20%	No	No	No	No
BRCA1	Yes > 60%	Yes 40-60%	Yes < 5%	No	
BRCA2	Yes > 60%	Yes 15-30%	Yes < 5%	No	Prostate: 33%
BRIP1	No	Yes 5-10%	No	No	No
CDH1	Yes (LBC) 40%	No	No	No	Diffuse gastric cancer: 35-45%
CHEK2	Yes 25-30%	No	No	Yes 15%	
PALB2	Yes 40-60%	Yes 3-5%	Yes 2-3%	No	No
PTEN	Yes 40%	No	No	Yes 10%	Thyroid: 20% Endometrial: 20%
RAD51C	Yes 20%	Yes 10%	No	No	No
RAD51D	Yes 10%	Yes 10%	No	No	No
STK11	Yes 40%	No	Yes 10-30%	Yes 30%	Gastric: 30% Sertoli-Leydig: 10-20%
TP53	Yes 40%	No	Possibly	Possibly	Sarcoma, brain, leukaemia, adrenocortical carcinoma

Lifetime risk in general "average risk" population: *BC 11%, †ovarian cancer 1.3%, ‡pancreatic cancer 1.6%, §colon cancer 4%
ATM, ATM serine/threonine kinase; *BARD1*, *BRCA1* associated ring domain 1; BC, breast cancer; *BRIP1*, *BRCA1* interacting helicase 1; *CDH1*, cadherin 1; *CHEK2*, checkpoint kinase 2; HBOC, hereditary breast and ovarian cancer syndrome; LBC, lobular breast cancer; *PALB2*, partner and localiser of *BRCA2*; *PTEN*, phosphatase and tensin homologue; *PV*, pathogenic variant; *RAD51C*, RAD51 paralogue C; *RAD51D*, RAD51 paralogue D; *STK11*, serine/threonine kinase 11; *TP53*, tumour suppressor protein p53

- Risk assessment should be comprehensive and individualised, taking into account the specific gene and variant identified, as well as other individual non-genetic (e.g. age, reproductive history) and genetic risk factors
- When available, validated tools such as CanRisk (https://www.canrisk.org/) should be used to aid decision making
- Counselling must include clear explanations of the familial implications, indicating which relatives (both female and male) need to be informed and offered counselling and testing
  - Enhancing awareness and availability of testing in at-risk relatives should be a priority

Follow-up

- Follow-up is life-long for individuals with HBOC and may involve serial imaging, risk-reducing surgery, risk-reducing medication and quality of life (QoL) issues
- Risk management should be performed in specialised high-risk clinics that are multidisciplinary and should include psychologists, if possible

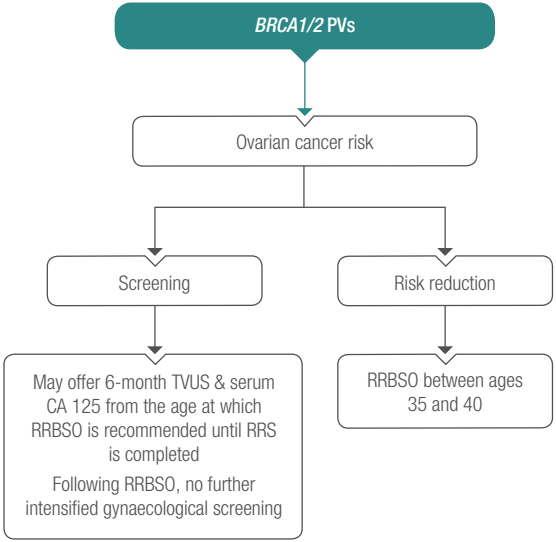
OVARIAN CANCER RISK MANAGEMENT

- Recommendations for ovarian cancer screening and risk reduction in carriers of *BRCA1* and *BRCA2* PVs are shown in the figure on the next page

Imaging and screening

- It remains unknown whether ovarian cancer screening improves survival in high-risk women
  - False positive results may lead to unnecessary surgery
  - Experienced sonographers can distinguish between benign and malignant ovarian tumours to avoid unnecessary surgeries
- Although of uncertain benefit, ovarian screening with transvaginal ultrasound (TVUS) every 6 months and serum cancer antigen 125 (CA 125) determination may be considered
  - If carried out, it should start at the age at which risk-reducing bilateral salpingo-oophorectomy (RRBSO) is offered, and should continue until RRBSO is carried out
  - The benefits of RRBSO as well as the limitations and potential harms of screening should be clearly communicated to patients
  - Screening should be provided in tertiary care or high-volume centres under structured screening protocols by experienced sonographers
- There is no evidence to support routine screening after RRBSO
- Large prospective clinical studies are ongoing to test promising non-invasive cancer biomarkers for screening and early cancer diagnosis

OVARIAN CANCER SCREENING AND RISK REDUCTION IN CARRIERS OF *BRCA1/2* PVs



CA 125, cancer antigen 125; PV, pathogenic variant; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRS, risk-reducing surgery; TVUS, transvaginal ultrasound

Lifestyle factors and risk-reducing medication

- Use of the oral contraceptive pill (OCP) is associated with a 40-60% lower risk of ovarian cancer
  - However, there are conflicting data on whether the OCP increases breast cancer (BC) risk amongst *BRCA1/2* PV carriers
- As PV carriers are encouraged to undergo RRBSO before the age at which ovarian cancer risk becomes relevant, the long-term clinical significance of OCP use as a risk-reduction measure for ovarian cancer is unclear

Risk-reducing surgery

- The most effective strategy for ovarian cancer risk reduction in *BRCA1/2* PV carriers is RRBSO
- RRBSO should include removal of both ovaries and fallopian tubes and should be reserved for patients at high risk of epithelial ovarian and fallopian tube cancer

- PV type, patient preferences and family history should be considered when deciding the timing of RRBSO
  - Undergoing RRBSO before the necessary age can have a negative impact on a woman's health including all the consequences of premature menopause
  - RRBSO should be delayed until an age when ovarian cancer risk is increased above that of the general population
- RRBSO should be carried out in women with *BRCA1/2* PVs who have completed childbearing at the following ages:
  - 35-40 years for *BRCA1* PV carriers
  - 40-45 years for *BRCA2* PV carriers
- RRBSO should be considered at age 45-50 years in women with *BRCA1* interacting helicase 1 *(BRIP1)*, RAD51 paralogue C *(RAD51C)* or RAD51 paralogue D *(RAD51D)* PVs who have completed childbearing
- RRBSO may also be considered for postmenopausal women with a *PALB2* PV
- For gynaecological risk-reducing surgery in Lynch syndrome [MutL homologue 1 *(MLH1)*, MutS homologue 2 *(MSH2)* or MutS homologue 6 *(MSH6)* PVs)], please refer to the ESMO Clinical Practice Guideline (CPG) for the management of hereditary gastrointestinal cancers (see: https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hereditary-gastrointestinal-cancers)
- The recommended surgical approach is minimally invasive surgery with a laparoscopic route to reduce morbidity and hospitalisation time, and to provide a better aesthetic outcome
- Pathological evaluation of the surgical specimen should include a Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) protocol
- Risk-reducing salpingectomy (bilateral salpingectomy alone or bilateral salpingectomy followed by delayed oophorectomy) is not recommended outside the setting of a clinical trial
- Hysterectomy is not routinely recommended at the time of RRBSO to reduce cancer risk unless other indications exist (e.g. *MLH1*, *MSH2* or *MSH6* PVs, other risk factors for endometrial cancer or benign uterine pathology)

Screening for additional malignancies

- Screening with annual contrast enhanced MRI and/or endoscopic US from age 50 (or 5-10 years younger than the affected relative) may be considered in *BRCA1*, *BRCA2*, ATM serine/threonine kinase *(ATM)*, tumour suppressor protein p53 *(TP53)* or *PALB2* carriers with at least one first- or second-degree relative with exocrine pancreatic cancer

COUNSELLING, RISK REDUCTION AND SCREENING IN THE PRESENCE OF OTHER MODERATE-HIGH RISK PATHOGENIC VARIANTS

- Genetic testing for HBOC susceptibility often incorporates screening for PVs in genes beyond *BRCA1* and *BRCA2*
  - The associated cancer risks vary widely between genes, as do the approaches to screening and risk reduction
  - It is important to differentiate "other genes" from *BRCA1* and *BRCA2* during counselling
- PVs in *BRIP1*, *RAD51C* and *RAD51D* are associated with ovarian cancer risks of ≥ 10%
- PVs in *PALB2* and *ATM* are associated with ovarian cancer risks of 3-5% and ≤ 3%, respectively
  - Premenopausal RRBSO is not routinely recommended for women with *PALB2* or *ATM* PVs, given this level of risk
  - In postmenopausal women with *PALB2* PV, RRBSO can be considered
- Checkpoint kinase 2 *(CHEK2)* PVs are not associated with an increased risk of ovarian cancer
- Validated risk assessment tools, such as CanRisk, may be used to aid individual risk management

REPRODUCTIVE AND ENDOCRINOLOGICAL ISSUES IN INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Contraception

- While hormone-based forms of contraception are not contraindicated, unaffected carriers should be offered non-hormonal forms of contraception when feasible and should minimise prolonged periods of exposure to exogenous hormones

Fertility

- Healthy female carriers should be encouraged to complete childbearing before the recommended age for RRBSO; if this is not feasible, oocyte and embryo cryopreservation can be offered at a young age
- Individuals with highly penetrant cancer susceptibility syndromes should be informed about prenatal diagnosis or preimplantation genetic testing (PGT), which may be used to avoid passing on the hereditary PV to future offspring
  - The pros and cons of these strategies should be clearly discussed, including potential pregnancy termination in the case of prenatal diagnosis and the need for *in vitro* fertilisation strategies with PGT
  - Religious, cultural, ethical and socioeconomic issues, as well as country/centre availability, are important factors affecting the individual's choice to access these technologies

Management of menopausal symptoms

- Healthy carriers undergoing RRBSO at a young age should be informed of the short- and long-term health consequences of premature menopause
- Hormone replacement therapy (HRT) may be considered after RRBSO in unaffected *BRCA1/2* PV carriers to alleviate menopausal symptoms
  - A recent study has suggested that the use of HRT in unaffected carriers aged > 45 years may be associated with an increased risk of BC
  - Short-term HRT may be offered after RRBSO
  - Longer-term use of HRT may be considered on a case-by-case basis for unaffected carriers aged > 45 years who have also previously undergone bilateral risk-reducing mastectomy
- The limitations and risks of HRT should be clearly communicated
- Local vaginal therapies, including low-dose intravaginal oestrogens, may be considered to manage the genitourinary symptoms of menopause

Bone health

- Bone assessment is recommended in women who have undergone premenopausal RRBSO, including:
  - Regular assessment of clinical risk factors for accelerated bone loss
  - Measurement of bone mineral density
- Preventive and therapeutic measures should be considered as indicated
  - Resistance and weight-bearing exercise, smoking cessation and reduced alcohol intake should be highly encouraged
  - Vitamin D and calcium supplements are recommended
  - Antiresorptive therapy should be considered whenever indicated

UNIQUE PSYCHOLOGICAL ISSUES FOR INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

- Observational studies of the psychological impact of HBOC have provided highly variable results
  - Some carriers experience elevated and sustained levels of psychological distress
  - Individual risk factors include high levels of anxiety and depression prior to genetic testing, cancer diagnosis, being unpartnered and a family history of cancer
- RRBSO can have a negative impact on sexual function
  - Effects include vaginal dryness and loss of sexual satisfaction
  - Sexual dysfunction can be long-lasting and is independent of menopausal status prior to RRBSO or use of HRT
- Sexual health concerns should be assessed, and support and resources should be offered to address sexual dysfunction
  - Individuals should be asked about sexual health concerns regardless of age, partner status or sexual orientation
- The need for further information and emotional support should be assessed before disclosure of genetic test results, and individuals should be offered referrals for psychological counselling and/or further support

PERSONALISED MEDICINE AND FUTURE DIRECTIONS

- Germline genetic testing has led to improvements in screening, risk reduction and therapies for those with inherited cancer susceptibility; however, there is a need for more individualised risk assessment to inform the timing and type of risk-reduction strategies, such as RRBSO, and for optimal risk management in moderate penetrance genes
- Single nucleotide polymorphisms (SNPs) have been well validated to alter cancer risk, both in the general population and in those with inherited cancer susceptibility
  - A polygenic risk score (PRS) captures the risk associated with SNPs and can be used in models such as CanRisk
  - Modification by PRS is likely to become increasingly important as individuals without a strong family history of cancer undergo genetic testing
- Early detection strategies using liquid biopsies targeting tumour-derived mutational, epigenetic or transcriptomic features is another emerging area with relevance to individuals with genetic susceptibility
  - If stage I ovarian cancer could be reliably detected, routine use and/or timing of RRBSO could be reconsidered
  - Avoiding surgery-induced menopause in women in their 30s could have a major impact on QoL and long-term bone and cardiac health outcomes
- Use of PRSs, interval salpingectomy, novel risk-reduction strategies and liquid biopsy assays for early detection should continue to be performed and assessed in the context of clinical trials

NON-EPITHELIAL OVARIAN CANCER

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

- Initial signs and symptoms are subacute pelvic pain, a feeling of pelvic pressure and menstrual irregularities
- Diagnostic work-up should include pelvic ultrasound (US), abdominopelvic computed tomography (CT), chest X-ray and positron emission tomography (PET) scan in selected cases [germ cell tumours (GCTs)]
- In young patients, serum human chorionic gonadotropin (hCG), α-fetoprotein (AFP) and lactate dehydrogenase (LDH) levels, complete blood count and liver and renal function tests are recommended
  - Inhibin B is also a useful marker for sex cord stromal tumours (SCSTs)
- If a gonadoblastoma is suspected, a preoperative karyotype should be obtained on all premenarche girls
- GCTs are grouped according to the 2014 World Health Organization (WHO) classification, as shown in the table below

WHO 2014 CLASSIFICATION OF GCTs

Dysgerminoma
YST
Embryonal carcinoma
Non-gestational choriocarcinoma
Mature teratoma
Immature teratoma
Mixed GCT

GCT, germ cell tumour; WHO, World Health Organization; YST, yolk sac tumour

- Primitive GCTs comprising undifferentiated germ cells and those with extra-embryonic differentiation are malignant
- Teratomas are the most common GCTs and they are mostly benign
- Rare malignant GCTs include somatic cancers arising in dermoids and monodermal teratomas

- In the elderly, non-dysgerminoma GCTs arise from epithelial ovarian cancer, usually endometrioid and clear cell carcinomas
- Primitive GCTs and immature teratomas are chemosensitive and eligible for fertility-sparing surgery; as such, correct pathological diagnosis by a gynaecological pathologist is essential
- Diagnosis can be made on conventional histological material, using the immunohistochemical markers spalt-like transcription factor 4 (SALL4), octamer-binding transcription factor 4 (OCT4) and sex-determining region Y-box transcription factor 2 (SOX2), as shown in the table below, and fluorescence *in situ* hybridisation for chromosome *12p*

IMMUNOHISTOCHEMISTRY OF PRIMITIVE GCTs

	SALL4	OCT3/4	SOX2
Dysgerminoma	+	+	-
YST	+	-	-
Embryonal carcinoma	+	+	+

GCT, germ cell tumour; OCT3/4, octamer-binding transcription factor 3/4; SALL4, spalt-like transcription factor 4; SOX2, sex-determining region Y-box transcription factor 2; YST, yolk sac tumour

- SCSTs and steroid cell tumours are heterogeneous, as shown in the table on the next page
- Neoplasms of pure ovarian stroma are mostly benign
- In morphologically ambiguous cases, an immunopanel of inhibin α, calretinin and forkhead box L2 (FOXL2), together with *FOXL2* (402C-G) mutational analysis can confirm the diagnosis of an adult granulosa cell tumour (AGCT)
- *DICER1* mutations also occur in SCST
- Small cell carcinomas of the ovary hypercalcaemic type (SCCOHTs) are the most common form of ovarian undifferentiated carcinomas in women < 40 years of age and the most common ovarian tumour associated with hypercalcaemia
- SWI/SNF-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4) immunohistochemistry (IHC) is sensitive and specific for SCCOHT diagnosis and is useful in the differential diagnosis of poorly differentiated ovarian tumours

WHO 2014 CLASSIFICATION OF SCSTS AND STEROID CELL TUMOURS

PURE STROMAL TUMOURS	PURE SEX CORD TUMOURS	MIXED SEX CORD STROMAL TUMOURS
Fibroma	Adult granulosa cell tumour	SLCTs • Well differentiated • Moderately differentiated - With heterologous elements • Poorly differentiated - With heterologous elements • Retiform - With heterologous elements
Cellular fibroma	Juvenile granulosa cell tumour	
Thecoma	Sertoli cell tumours	
Luteinized thecoma associated with sclerosing peritonitis	Sex cord tumour with annular tubules	
Fibrosarcoma		SCSTs, NOS
Sclerosing stromal tumour		
Signet-ring stromal tumour		
Microcystic stromal tumour		
Leydig cell tumour		
Steroid cell tumour		
Steroid cell tumour, malignant		

NOS, not otherwise specified; SCST, sex cord-stromal tumour; SLCT, Sertoli-Leydig cell tumour; WHO, World Health Organization

STAGING AND RISK ASSESSMENT

Prognostic factors

- Staging is according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) classification for epithelial ovarian cancer, as shown in the table opposite
- Clinical prognostic factors are not well defined for ovarian GCTs; adverse factors include age > 45 years, stage > I, incomplete surgical resection and yolk sac tumour (YST) histology
- FIGO stage and intraperitoneal tumour rupture are the most common prognostic factors for SCSTs
- Prognosis of SCCOHT is poor and potential favourable prognostic factors are earlier stage (IA vs. other stages), age > 30 years, normal preoperative calcium level, tumour size < 10 cm, absence of large cells and complete surgical resection including bilateral oophorectomy

OVARIAN CANCER STAGING ACCORDING TO FIGO 2014 AND CORRESPONDING TNM STAGE

TNM STAGE	FIGO STAGE	DESCRIPTION
T1a N0 M0	Stage IA	Tumour limited to one ovary (capsule intact), no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings; no regional lymph node metastasis; no distant metastasis
T1b N0 M0	Stage IB	Tumour limited to both ovaries (capsules intact), no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings; no regional lymph node metastasis; no distant metastasis
T1c N0 M0	Stage IC1	Tumour limited to one or both ovaries with capsule ruptured (surgical spill); no regional lymph node metastasis; no distant metastasis
	Stage IC2	Tumour limited to one or both ovaries with capsule ruptured before surgery or tumour on ovarian surface; no regional lymph node metastasis; no distant metastasis
	Stage IC3	Tumour limited to one or both ovaries with malignant cells in ascites or peritoneal washings; no regional lymph node metastasis; no distant metastasis
T2a N0 M0	Stage IIA	Extension and/or implants on the uterus and/or tube(s); no malignant cells in ascites or peritoneal washings; no regional lymph node metastasis; no distant metastasis
T2b N0 M0	Stage IIB	Extension to and/or implants in other pelvic tissues; no malignant cells in ascites or peritoneal washings; no regional lymph node metastasis; no distant metastasis
T1/T2 N1 M0	Stage IIIA1	Tumour limited to the ovaries [one or both (T1) or tumour involves one or both ovaries with pelvic extension (T2)]; regional lymph node metastasis; no distant metastasis
	Stage IIIA1 (i)	Metastasis ≤ 10 mm in greatest dimension
	Stage IIIA1 (ii)	Metastasis > 10 mm in greatest dimension
T3a N0/N1 M0	Stage IIIA2	Microscopic peritoneal metastasis beyond the pelvis (no macroscopic tumour); no regional lymph node metastasis (N0) or regional lymph node metastasis (N1); no distant metastasis
T3b N0/N1 M0	Stage IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension; no regional lymph node metastasis (N0) or regional lymph node metastasis (N1); no distant metastasis

TNM STAGE	FIGO STAGE	DESCRIPTION
T3c N0/N1 M0	Stage IIIC	Macroscopic peritoneal metastasis beyond the pelvis > 2 cm in greatest dimension and/or regional lymph node metastasis; no regional lymph node metastasis (N0) or regional lymph node metastasis (N1); no distant metastasis
Any T Any N M1	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)

FIGO, International Federation of Gynecology and Obstetrics; M, metastasis; N, node; T, tumour; TNM, tumour–node–metastasis

Staging

- Open or minimally invasive surgery is required and staging includes infracolic omentectomy, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum and peritoneal washings in macroscopic stage I disease

GCTs

- Potential nodal metastasis should be cured by adjuvant chemotherapy (ChT)
- Nodal debulking surgery is required in rare cases of residual disease after ChT
- In early-stage disease not requiring adjuvant ChT, nodal dissection is indicated only when there is evidence of nodal abnormalities during surgical exploration and/or initial CT scan (lymphadenopathy)
- Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus is standard for young patients with GCTs
- Conservative management should also be considered for advanced disease because of tumour ChT sensitivity
- Systematic ovarian biopsy is not necessary when the contralateral ovary is macroscopically normal
- In young patients with macroscopic bilateral ovarian disease, preservation of a healthy part of one ovary and the uterus should be encouraged
- For postmenopausal women and those with advanced-stage disease or bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) should be conducted with careful surgical staging

SCSTs

- For patients of child-bearing age with SCSTs, preservation of the uterus and contralateral ovary is safe in macroscopic stage IA disease but should not be conducted in stages > I
- Conservative surgery is an option for young patients with stage I SCSTs, but its use in stage IC juvenile granulosa cell tumours remains controversial
- When conservative treatment is conducted, an endometrial curettage (or hysterectomy in the case of radical management) is necessary to rule out concomitant uterine cancers for patients with granulosa cell tumours
- Retroperitoneal evaluation is not mandatory because of the low incidence of retroperitoneal metastases in early-stage disease
- For postmenopausal women and those with advanced-stage disease or bilateral ovarian involvement, abdominal hysterectomy and BSO should be conducted with careful surgical staging

SCCOHTs

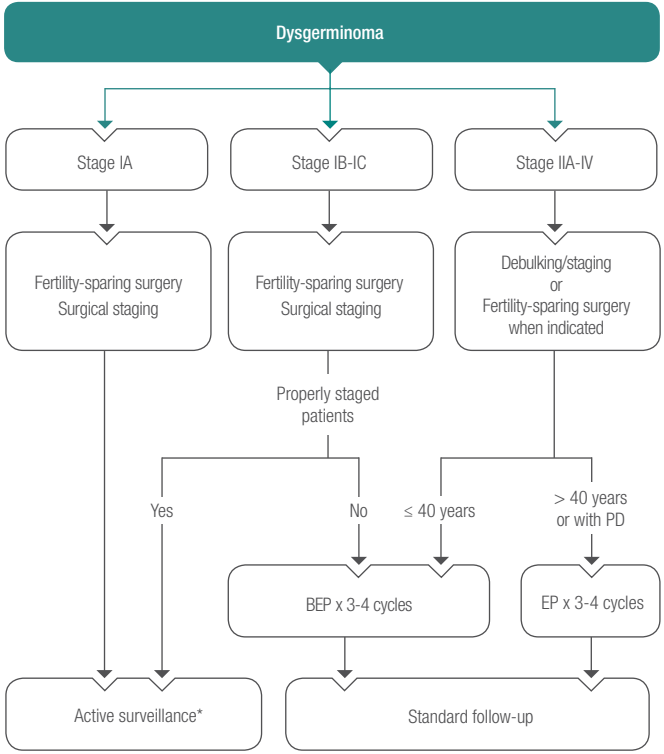
- Suspected cases should be reviewed by an expert pathologist and discussed in a specialised tumour board
- Conventional surgical treatment includes radical surgery (BSO and hysterectomy) combined with peritoneal and nodal staging surgery, even for macroscopically stage I disease
- Postoperative adjuvant treatment combines ChT and radiotherapy (RT)

MANAGEMENT OF EARLY NON-EPITHELIAL OVARIAN CANCER

Germ cell tumours

- In stage I disease, fertility-sparing surgery is safe with excellent long-term survival and has outcomes similar to patients undergoing hysterectomy with BSO
- Stage IA and properly staged stage IB-IC pure dysgerminoma should be treated with surgery alone, as shown in the figure on the next page

MANAGEMENT OF GCTs OF THE OVARY – DYSGERMINOMA

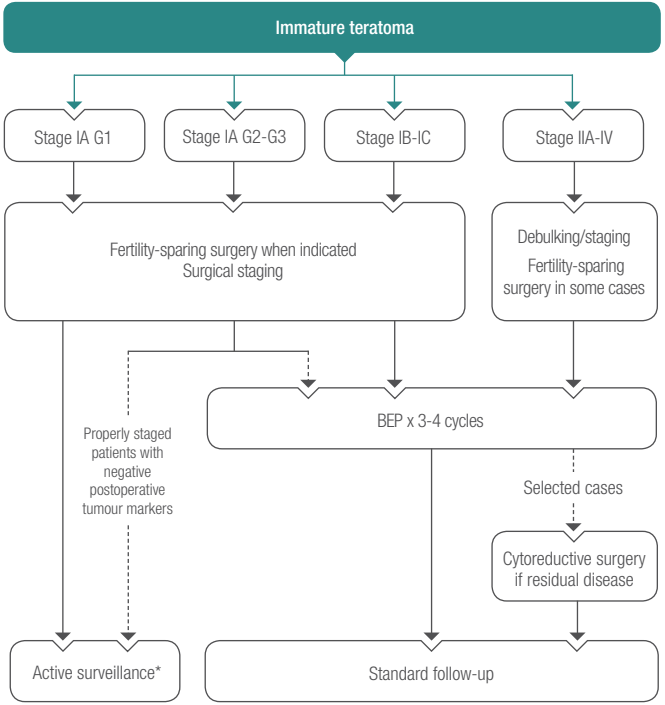


*See table on page 65

BEP, bleomycin–etoposide–cisplatin; EP, etoposide–cisplatin; GCT, germ cell tumour; PD, pulmonary disease

- Adjuvant ChT is not required for stage IA grade 1 immature teratomas after adequate surgical staging, as shown in the figure opposite
  - Adjuvant ChT in stage IA grade 2-3 and stage IB-IC is still controversial

MANAGEMENT OF GCTs OF THE OVARY – IMMATURE TERATOMA



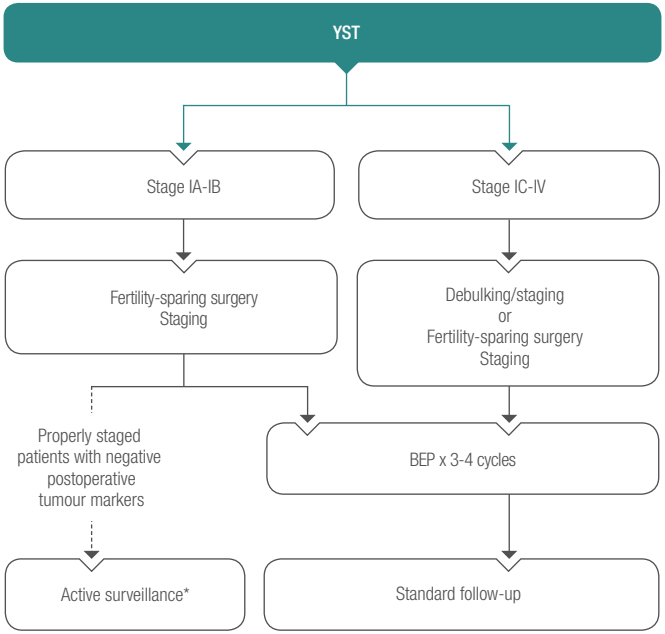
Dashed lines represent optional management approaches

*See table on page 65

BEP, bleomycin–etoposide–cisplatin; G, grade; GCT, germ cell tumour

- The use of close surveillance following fertility-sparing surgery for all grades of immature teratoma and stage I dysgerminoma is not universally accepted and needs to be discussed with the patient

MANAGEMENT OF GCTs OF THE OVARY – YST



Dashed lines represent optional management approaches

*See table on page 65

BEP, bleomycin–etoposide–cisplatin; GCT, germ cell tumour; YST, yolk sac tumour

- Stage I YSTs require adjuvant ChT after surgery, as shown in the figure above. Active surveillance can be considered for patients with stage I YSTs with complete staging and negative postoperative AFP, but this approach is not universally accepted and needs to be discussed with the patient
- The most commonly used combination is the 5-day bleomycin–etoposide–cisplatin (BEP) regimen
- Close and active surveillance, as shown in the table opposite, is required in cases where ChT is not administered

ACTIVE SURVEILLANCE PROGRAMME IN THE MANAGEMENT OF OVARIAN GCTs

TIME PERIOD	EXAMINATION	PELVIC US	TUMOUR MARKERS	CHEST X-RAY	CT CHEST ABDOMEN PELVIS
1st year	Monthly	2-monthly	Every 2 weeks (first 6 months) and then monthly	2-monthly	1 month* 3 months† 12 months
2nd year	2-monthly	4-monthly	2-monthly	4-monthly	–
3rd year	3-monthly	6-monthly	3-monthly	6-monthly	–
4th year	4-monthly	–	4-monthly	8-monthly	–
5th-10th year	6-monthly	–	6-monthly	Annually	–

*If not carried out preoperatively

†If clear, second-look laparoscopy if inadequate staging/immature teratoma

CT, computed tomography; GCT, germ cell tumour; US, ultrasound

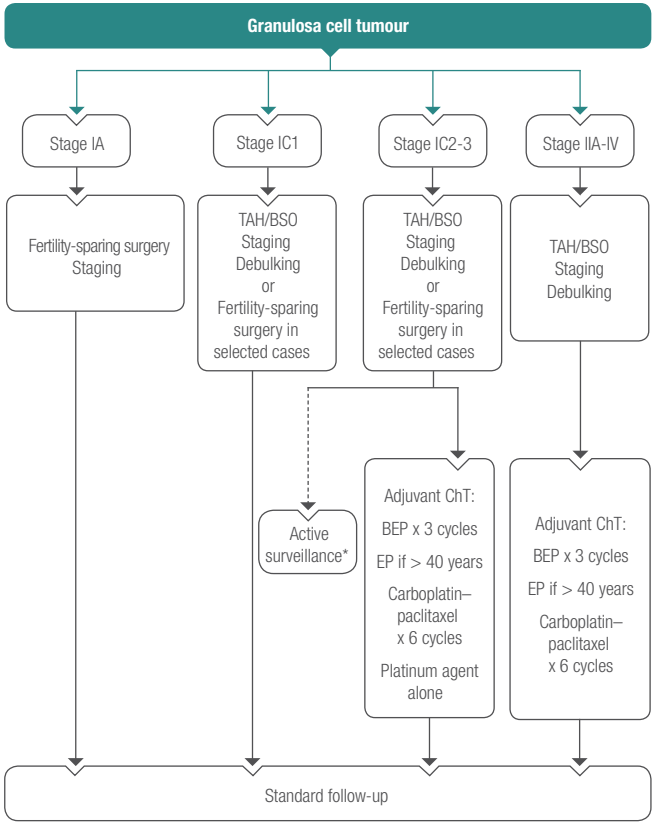
Suggested surveillance programme based on Mount Vernon proposal. Modified from: Vazquez I et al. Curr Opin Oncol 2013;25(5):539-45, with permission

- Patient adherence to scheduled visits is essential and patients should be advised against pregnancy in the first 2 years after initial diagnosis when relapse is most likely

Sex cord stromal tumours

- Stage IA granulosa cell tumours have an excellent prognosis after surgery alone and do not require adjuvant therapy, as shown in the figure on the next page
- The benefit of adjuvant ChT has yet to be demonstrated for patients with early-stage SCST, although platinum-based adjuvant ChT is an option for juvenile granulosa tumour stage IC and the use of adjuvant ChT can also be discussed with patients with stage IC2 AGCT
- The most commonly used regimen is BEP, with alternative options including carboplatin–paclitaxel (TC), etoposide–cisplatin (EP), cyclophosphamide–doxorubicin–cisplatin (CAP) or a platinum agent alone
- Bleomycin should not be administered to patients > 40 years old or those with pre-existing pulmonary disease (PD)
- In Sertoli-Leydig cell tumours (SLCTs), postoperative adjuvant ChT should be considered for patients with stage I poorly differentiated disease or disease with heterologous elements, as shown in the figure on page 67

MANAGEMENT OF SCSTs OF THE OVARY – GRANULOSA CELL TUMOUR

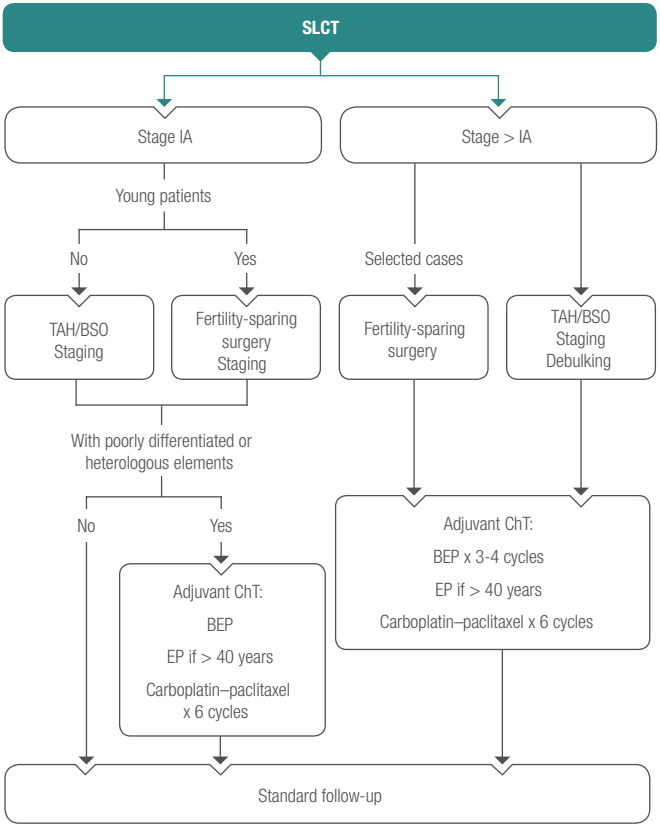


Dashed lines represent optional management approaches

*See table on page 65

BEP, bleomycin–etoposide–cisplatin; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; EP, etoposide–cisplatin; SCST, sex cord stromal tumour; TAH, total abdominal hysterectomy

MANAGEMENT OF SCSTs OF THE OVARY – SLCT



BEP, bleomycin–etoposide–cisplatin; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; EP, etoposide–cisplatin; SCST, sex cord stromal tumour; SLCT, Sertoli-Leydig cell tumour; TAH, total abdominal hysterectomy

Small cell carcinomas of the ovary hypercalcaemic type

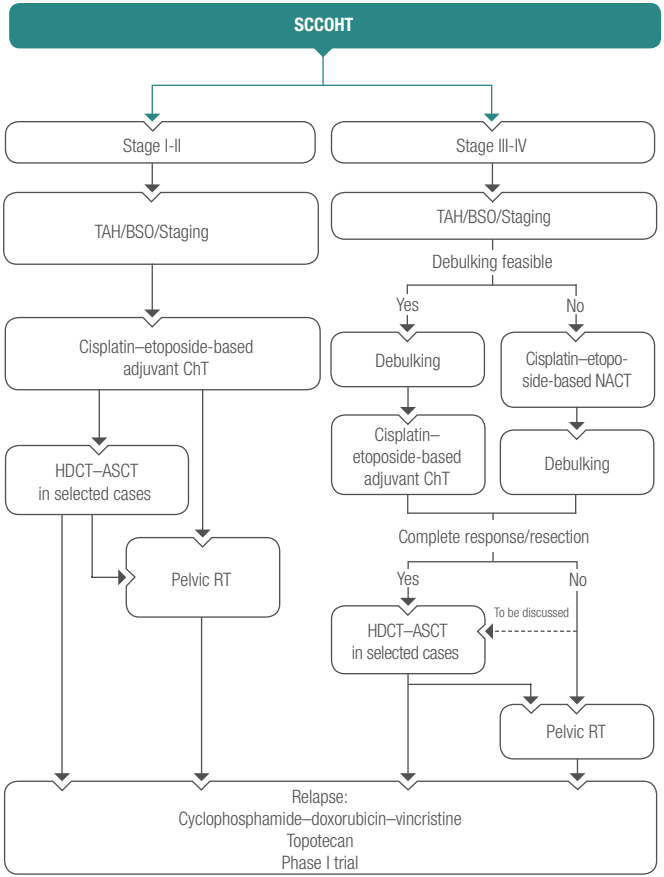
- In the absence of an international consensus for SCCOHT treatment, a multimodal approach including ChT, radical surgery and possibly RT is often proposed, as shown in the figure opposite
- A combination of a cisplatin–etoposide-based therapy is generally considered most appropriate
- For patients achieving a complete response (CR) after surgery and/or ChT, autologous stem cell transplantation (ASCT)-supported high-dose ChT (HDCT) is associated with better survival

MANAGEMENT OF ADVANCED NON-EPITHELIAL OVARIAN CANCER

Germ cell tumours

- Fertility-sparing surgery should be considered in advanced-stage disease as cure rates remain high
- Surgery should be moderated to avoid delays in postoperative ChT
- Platinum-based ChT is standard, with 5-day BEP being the most widely used regimen; 3 cycles are used for completely resected stage I disease and 4 cycles for more advanced disease
- Bleomycin should not be administered to patients > 40 years of age or those with pre-existing PD, given the risk of drug-related lung injury
- Alternative ChT regimens, such as cisplatin–vincristine–methotrexate–bleomycin–actinomycin D–cyclophosphamide–etoposide (POMB–ACE) and carboplatin–bleomycin–vincristine–cisplatin (CBOP)–BEP, have shown high activity, particularly in patients with high-risk disease, but have not been compared in randomised trials with BEP
- In platinum-sensitive relapse (progression > 4-6 weeks after ChT completion), second-line treatments include ifosfamide–platinum ± paclitaxel, vinblastine–ifosfamide–cisplatin (VeIP) and cisplatin–vinblastine–bleomycin (PVB)
- Patients with tumours that are resistant to platinum may receive salvage therapy with vincristine–actinomycin D–cyclophosphamide (VAC), paclitaxel–gemcitabine or gemcitabine–oxaliplatin
- HDCT for recurrent ovarian GCTs may result in durable and prolonged remissions, although data are scarce
- Any resectable residual disease should be removed, particularly for patients with normal serum marker in which residual disease is present on imaging after adjuvant therapy and for patients with immature teratomas
- Secondary cytoreductive surgery for recurrent/progressive ovarian GCT remains controversial

MANAGEMENT OF SCCOHT



Dashed lines represent optional management approaches

ASCT, autologous stem cell transplantation; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; HDCT, high-dose chemotherapy; NACT, neoadjuvant chemotherapy; RT, radiotherapy; SCCOHT, small cell carcinoma of the ovary hypercalcaemic type; TAH, total abdominal hysterectomy

Sex cord stromal tumours

- Debulking surgery, when feasible, remains the most effective treatment for metastatic or recurrent granulosa cell tumours
- Platinum-based ChT is recommended for advanced-stage SCSTs or recurrent disease
- BEP (3 cycles) or TC (6 cycles) are recommended for adjuvant postoperative ChT and for patients with recurrent SCSTs
- Steroid cell tumours that are pleomorphic, large, at an advanced stage or with non-operable residual disease or with an increased mitotic count should be treated with postoperative BEP (if not used previously) or a taxane–platinum combination
  - Alternative regimens include PVB, EP, CAP, VAC and weekly paclitaxel for patients relapsing after platins
- ChT may be useful for patients with persistent SLCTs
- Hormone therapy is a useful alternative for patients with advanced-stage or recurrent AGCTs
- Antiangiogenic agents have also been investigated in recurrent AGCT and are currently being evaluated in clinical trials

Small cell carcinomas of the ovary hypercalcaemic type

- In bulky stage III or stage IV disease, where primary debulking surgery is considered unachievable, neoadjuvant ChT (NACT) can be considered on an individual patient basis after discussion within a tumour board
- A cisplatin–etoposide-based therapy is considered most appropriate
- For patients achieving a CR after surgery and/or ChT, ASCT-supported HDCT may be associated with better prognosis
- Regimens used for relapsed disease include cyclophosphamide–doxorubicin–vincristine, with some activity also being reported for carboplatin–paclitaxel and topotecan
- Beyond second-line treatment, patients with a good performance status (PS) should be considered for Phase I trials

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Response evaluation and follow-up programme after chemotherapy

GCTs

- Serum tumour markers (hCG, AFP, LDH, cancer antigen 125 and inhibin B) can accurately correlate with tumour response during ChT
- A CT scan of the abdomen, pelvis and chest (if lung metastases are suspected) along with pelvic US can be used to evaluate response to ChT in patients with measurable disease

- Most women with GCTs have excellent survival outcome so the side-effects of treatment, particularly long-term effects, need to be considered, as shown in the table below

TOXICITY OF BEP AND LONG-TERM COMPLICATIONS

TOXICITY/COMPLICATION
Pulmonary toxicity, decreased DLCO
AML
Neuropathy
Raynaud disease
Tinnitus
High-tone hearing loss
Gonadal dysfunction
Cardiovascular disease/hypertension
Nephrotoxicity
Osteoporosis after radical surgery in young patients

AML, acute myeloid leukaemia; BEP, bleomycin–etoposide–cisplatin; DLCO, diffusing capacity for carbon monoxide

- The low numbers of cases investigated means that the risk of ChT in the development of secondary malignancies cannot be assessed
- Follow-up visits must include history, physical and pelvic examinations and exploration of tumour markers every 3 months for the first 2 years, every 6 months during the third year (stopping tumour marker investigation in the third year) and then yearly until progression

SCSTs

- SCSTs have a tendency for late recurrence so long-term follow-up is required
- Follow-up visits, including physical examination and tumour marker exploration, must be carried out every 6 months indefinitely
- Pelvic US is recommended every 6 months for patients undergoing fertility-sparing surgery, with CT scan or magnetic resonance imaging (MRI) conducted when clinically indicated
- The use of PET scanning is not recommended

Fertility preservation in non-epithelial ovarian cancer

- Fertility outcome depends on the ChT given and on patient age, with younger patients having greater reserves of oocytes
- The likelihood of ChT-induced amenorrhoea is based on the type of ChT used, its cumulative dose and the duration of therapy
- The cumulative probability of achieving pregnancy after treatment is higher in women receiving ≤ 3 cycles of cisplatin compared with those receiving > 3 cycles
- Oocyte cryopreservation is an option for women scheduled to receive ChT, either by postponing cancer treatment to enable ovulation induction and oocyte aspiration, or by controlled ovarian hyperstimulation followed by oocyte cryopreservation 12 months after the end of ChT

Hormone replacement therapy and contraception

- ChT can lead to ovarian dysfunction and sterility
- At 10 years of follow-up, despite some sequelae of treatment, survivors of GCT have a healthy life comparable to that of controls
- Hormone replacement therapy can be used for patients with GCTs but should be avoided for those with granulosa cell tumours and other sex cord stromal malignancies, which are thought to be hormone dependent

EPITHELIAL OVARIAN CANCER

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnostic work-up

- The standard work-up for patients with suspected epithelial ovarian cancer (EOC) should include detailed history and clinical examination with relevant laboratory and imaging tests, as shown in the table below
  - This includes serum cancer antigen 125 (CA 125) measurement, pelvic ultrasound by an expert examiner and computed tomography (CT) scan of the thorax, abdomen and pelvis

DIAGNOSTIC WORK-UP OF EOC

• Detailed history and clinical examination
• Serum CA 125
• Serum CEA and CA 19-9 in the case of MC, and endoscopy if either or both are elevated
• Transabdominal and transvaginal US by expert examiner
• CT of thorax, abdomen and pelvis
• Pathological examination of adequate tumour sample from diagnostic biopsy or surgical specimen
• Cytological assessment of pleural effusion if present

CA 19-9, carbohydrate antigen 19-9; CA 125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, computed tomography; EOC, epithelial ovarian cancer; MC, mucinous carcinoma; US, ultrasound

Pathology and molecular biology

- Pathological diagnosis should be made according to the 2020 World Health Organization (WHO) classification by an expert gynaecological pathologist
  - The WHO classification recognises at least five distinct subtypes of malignant EOC, including high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear cell carcinoma (CCC), low-grade serous carcinoma (LGSC) and mucinous carcinoma (MC)
  - Immunohistochemistry staining patterns and molecular features of the different subtypes are summarised in the table on the next page
- All patients with high-grade ovarian cancer should be tested for germline and/or somatic *BRCA1/2* mutations at diagnosis
- Testing for homologous recombination deficiency (HRD) is recommended in advanced high-grade cancers

PATHOLOGY AND MOLECULAR BIOLOGY OF EOC SUBTYPES

		HGSC	EC	CCC	LGSC	MC
IHC staining	p53	abnormal	abnormal/normal	normal	normal	normal
	p16	+	-	-		
	WT-1	+	-	-	+	-
	ER	+/-	+	-	+	-
	PAX8	+	+		+	-
	Vimentin		+			
	HNF1β			+		
	CDX2					+
Molecular alterations (decreasing prevalence from top to bottom)		*TP53* *BRCA1/2* HRD	*CTNNB1* *ARID1A* *PTEN* *KRAS* *TP53* (high-grade EC) MSI/dMMR	*ARID1A* *PI3KCA* *PTEN* MSI/dMMR	*KRAS* *BRAF* *RAF* *CDKN2A* *KRAS* *HER2*	*CDKN2A* *KRAS* *HER2*

ARID1A, AT-rich interaction domain 1A; ***BRAF***, B-Raf proto-oncogene; CCC, clear cell carcinoma; ***CDKN2A***, cyclin-dependent kinase inhibitor 2A; CDX2, homeobox protein CDX-2; C***TNNB1***, catenin beta-1; dMMR; mismatch repair deficiency; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; ER, oestrogen receptor; ***HER2***, human epidermal growth factor receptor 2; HGSC, high-grade serous carcinoma; HNF1β, hepatocyte nuclear factor-1beta; HRD, homologous recombination deficiency; IHC, immunohistochemistry; ***KRAS***, Kirsten rat sarcoma virus; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; MSI, microsatellite instability; PAX8, paired box gene 8; ***PI3KCA***, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ***PTEN***, phosphatase and tensin homologue; ***RAF***, Raf proto-oncogene; ***TP53***, tumour suppressor protein p53; WT-1, Wilms tumour 1

STAGING AND RISK ASSESSMENT

- Surgical staging of EOC should be according to the revised 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system, as shown in the table on the opposite page
- The histotype and primary tumour site should be established and recorded as part of routine staging for treatment planning
- If the disease appears suitable for cytoreduction on imaging, and there are no surgical or medical contraindications, surgical staging should be carried out to explore the extent of disease in the abdomino-peritoneal cavity and assess the likelihood of achieving optimal cytoreduction

STAGING OF EOC ACCORDING TO THE REVISED 2014 FIGO SYSTEM

Stage I: Tumour confined to ovaries or fallopian tube(s)	
IA	Tumour limited to one ovary (capsule intact) or fallopian tube without tumour on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes without tumour on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings
IC IC1 IC2 IC3	Tumour limited to one or both ovaries or fallopian tubes with any of the following: Surgical spill Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
Stage III: Tumour involves one or both ovaries or fallopian tubes or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal LNs	
IIIA1 IIIA1(i) IIIA1(ii)	Positive retroperitoneal LNs only (cytologically or histologically proven): Metastasis ≤ 10 mm in greatest dimension Metastasis > 10 mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal LNs
IIIB	Macroscopic peritoneal metastasis beyond the pelvis ≤ 2 cm in greatest dimension with or without metastasis to the retroperitoneal LNs
IIIC	Macroscopic peritoneal metastasis beyond the pelvis > 2 cm in greatest dimension with or without metastasis to the retroperitoneal LNs (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV: Distant metastasis excluding peritoneal metastases	
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal LNs and LNs outside of the abdominal cavity)

EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node
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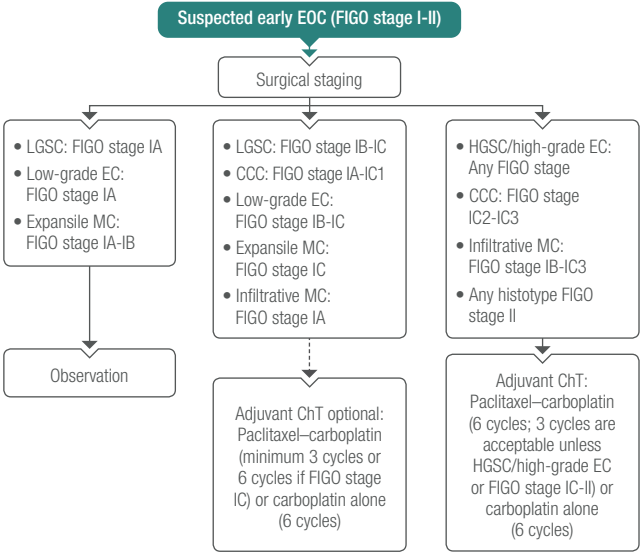
MANAGEMENT OF EARLY EPITHELIAL OVARIAN CANCER

- A treatment algorithm for the management of early EOC (FIGO stage I-II) is shown in the figure below

MANAGEMENT OF EARLY EOC (FIGO STAGE I-II)



The dashed line indicates optional treatments

CCC, clear cell carcinoma; ChT, chemotherapy; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma

Surgery

- The aim of surgery for early EOC is complete resection of the tumour and adequate staging, including:
  - Midline laparotomy
  - Inspection and palpation of the whole abdominal cavity
  - Peritoneal washing with cytological examination
  - Biopsies from all visible lesions and all abdominal fields
  - Bilateral salpingo-oophorectomy
  - Hysterectomy
  - Omentectomy
  - Appendicectomy in MC
  - Systematic pelvic and para-aortic lymphadenectomy
- The role of laparoscopic surgery is under debate and midline laparotomy remains the standard procedure
- Fertility-sparing surgery can be considered in young patients following discussion with the patient about potential risks
  - Contralateral ovary and uterus preservation can be considered for patients with any stage IA histotype or stage IC1-2 EOC with unilateral ovarian involvement and a favourable histology (i.e. low-grade tumours)
- Surgical staging provides prognostic information and defines whether systemic therapy is needed
  - Systematic pelvic and para-aortic lymphadenectomy for staging purposes is recommended for high-grade histologies

Systemic therapy

- The benefit of adjuvant chemotherapy (ChT) in patients with EOC according to histology, grade and FIGO stage is summarised in the table below

SUMMARY OF BENEFIT OF ADJUVANT CHT FOR EARLY EOC (FIGO STAGE I-II)

	FIGO STAGE			
Histology and grade	IA	IB-IC1	IC2-IC3	II
HGSC	Yes	Yes	Yes	Yes
LGSC	No	Consider	Consider	Yes
CCC	Consider	Consider	Yes	Yes
High-grade EC	Yes	Yes	Yes	Yes
Low-grade EC (grade 1-2)	No	Consider	Consider	Yes
Expansile MC	No	No for IB Consider for IC1	Consider	Yes
Infiltrative MC	Consider	Yes	Yes	Yes

"Yes" indicates that benefit of adjuvant systemic therapy has been observed. "No" indicates no evidence of benefit. "Consider" indicates that there may be a benefit and adjuvant systemic therapy can be considered

CCC, clear cell carcinoma; ChT, chemotherapy; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; FIGO, International Federation of gynecology and Obstetrics; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinom

- Adjuvant ChT in early-stage EOC is generally recommended for patients with FIGO stage I-IIB disease (see exceptions shown in the table on the previous page)
  - Adjuvant ChT comprises either paclitaxel–carboplatin or carboplatin alone (six cycles)
  - For patients receiving paclitaxel–carboplatin, a minimum of three cycles are recommended except for HGSC/high-grade endometrioid carcinoma or any stage IC to stage II regardless of histotype, for which six cycles are suggested

MANAGEMENT OF ADVANCED EPITHELIAL OVARIAN CANCER

- A treatment algorithm for the management of advanced EOC (FIGO stage III-IV) is shown in the figure on the opposite page

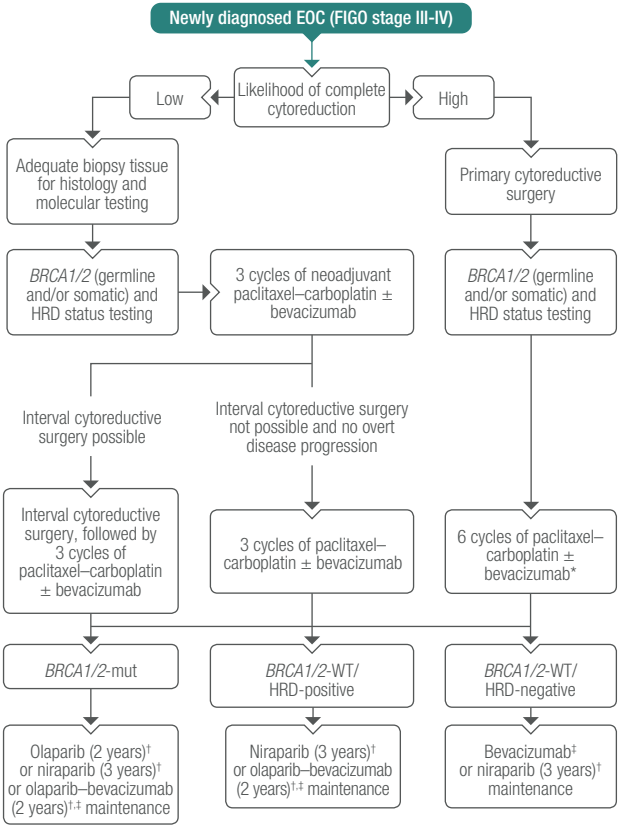
Surgery

- For patients with stage III-IV EOC who are physically able to undergo surgery and for whom complete resection seems achievable, primary cytoreductive surgery (PCS) is recommended, followed by systemic treatment
  - Patients should be evaluated for PCS by a specialised team with the aim of achieving complete cytoreduction (absence of all visible residual disease)
- PCS is also recommended for patients with less chemo-sensitive tumour subtypes (e.g. MC or LGSC), even if achieving complete resection is uncertain and a small residual tumour (< 1 cm) may remain
- When complete cytoreductive surgery is not feasible, adequate biopsy tissue should be obtained for histology and molecular testing
  - In these patients, neoadjuvant ChT for three cycles followed by interval cytoreductive surgery (ICS) and three cycles of paclitaxel–carboplatin are recommended
  - Bevacizumab in the neoadjuvant setting, before ICS, can be considered
  - When ICS is not possible, and in the absence of overt disease progression, three additional cycles of paclitaxel–carboplatin alone or with bevacizumab are recommended

Systemic therapy

- Systemic therapy decisions should be informed by *BRCA1/2* (germline and/or somatic) and HRD status testing carried out at primary diagnosis
- Paclitaxel (175 mg/m^2)–carboplatin [area under the curve (AUC) 5-6] every 3 weeks for six cycles is the standard first-line ChT for patients with advanced ovarian cancer
- The schedule of weekly ChT with paclitaxel (60 mg/m^2)–carboplatin (AUC 2) can be considered as an alternative in frail patients
- The combination of carboplatin with docetaxel or pegylated liposomal doxorubicin (PLD) can be considered in patients with contraindications to paclitaxel

MANAGEMENT OF ADVANCED EOC (FIGO STAGE III-IV)



*Weekly ChT with paclitaxel (60 mg/m^2)–carboplatin (AUC 2) can be an alternative in frail patients

†Only when patients have complete or partial response to platinum or no evidence of disease. For patients without response to platinum, PARPis are not indicated; these patients can be managed with bevacizumab maintenance if appropriate (mainly stable disease) or with second-line therapy if they have progressive disease (see figure on page 81)

‡Option for patients for whom bevacizumab was added to paclitaxel–carboplatin. Bevacizumab as maintenance therapy should be given for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier

AUC, area under the curve; ChT, chemotherapy; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; mut, mutated; PARPi, poly (ADP-ribose) polymerase inhibitor; WT, wild type

- Bevacizumab improves progression-free survival (PFS) in patients with stage III-IV EOC and should be considered in addition to paclitaxel–carboplatin
- Intraperitoneal (IP) ChT and hyperthermic IP perioperative ChT are not considered a standard of care in the first-line setting

Maintenance treatment

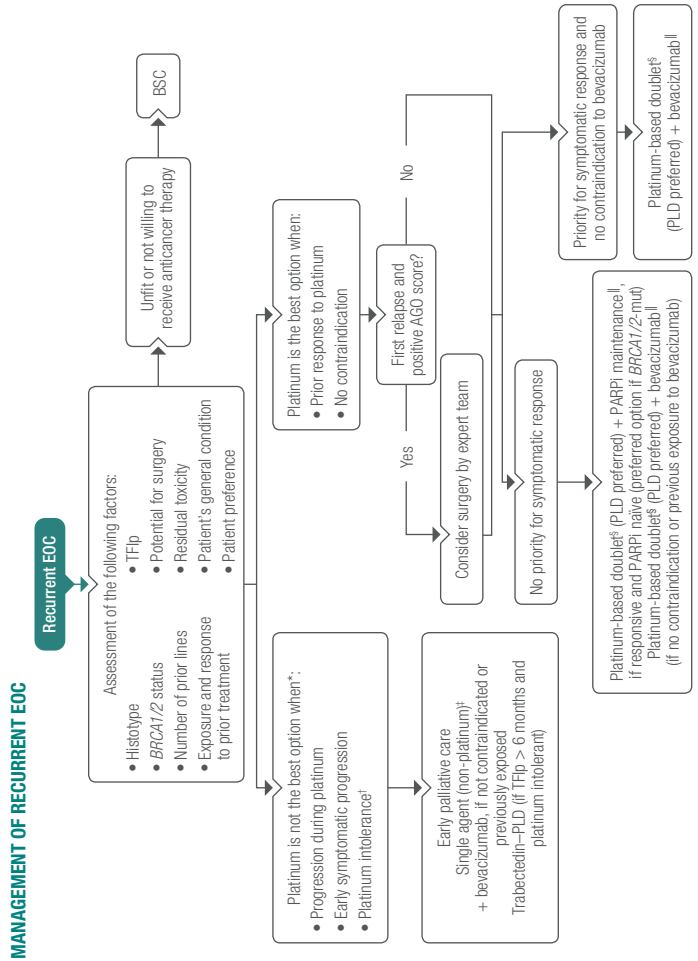
- Maintenance treatment with poly (ADP-ribose) polymerase inhibitors (PARPis), with or without bevacizumab, is recommended for patients with *BRCA1/2*-mutated (mut) or *BRCA1/2*-wild type (WT)/HRD-positive tumours with no evidence of disease at the end of ChT or a complete or partial response to platinum–paclitaxel first-line ChT
  - For *BRCA1/2*-mut: Olaparib for 2 years, niraparib for 3 years or olaparib for 2 years in combination with bevacizumab for up to 15 months
  - For *BRCA1/2*-WT/HRD-positive: Niraparib for 3 years or olaparib for 2 years in combination with bevacizumab for up to 15 months
- Maintenance treatment with either bevacizumab for up to 15 months or niraparib for 3 years can be recommended for HRD-negative tumours, with the latter following complete or partial response to platinum–paclitaxel first-line ChT. The choice of treatment should be based on patient disease and clinical characteristics
- Maintenance with anti-oestrogen therapy after first-line platinum-based ChT can be considered in patients with LGSC

MANAGEMENT OF RECURRENT EPITHELIAL OVARIAN CANCER

- A treatment algorithm for the management of recurrent EOC is shown in the figure opposite
- The following should be assessed when selecting treatment for patients with recurrent EOC:
  - Histotype
  - *BRCA1/2* status
  - Number of prior lines of treatment
  - Exposure and response to prior treatment
  - Treatment-free interval from last platinum
  - Possibility of achieving a complete secondary surgical cytoreduction
  - Residual ChT toxicity
  - The patient's general condition and preferences

Surgery

- Patients with first relapse of EOC after > 6 months of last platinum administration should be evaluated by a gynaecological oncology centre with experience in ovarian cancer surgery to identify potential candidates for surgical cytoreduction



*Patient choice and quality of life issues may also suggest that platinum is not the best option

†In patients with platinum intolerance who have relapsed > 6 months from previous platinum, the combination of trabectedin and PLD may be recommended (EMA approved, not FDA approved)

‡Weekly paclitaxel, PLD, topotecan or gemcitabine

§Paclitaxel, PLD or gemcitabine

‖Bevacizumab or PARPi until disease progression or next line of treatment is started

AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; BSC, best supportive care; EMA, European Medicines Agency; EOC, epithelial ovarian cancer; FDA, Food and Drug Administration; mut, mutated; PARPi, poly (ADP-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TFIp, treatment-free interval from last platinum

Platinum-based systemic therapy

- Patients who have previously responded to platinum-based ChT without early symptomatic relapse should be treated with either a platinum-based doublet (PLD, gemcitabine or paclitaxel; usually four to six cycles) with bevacizumab or a platinum doublet followed by maintenance PARPi therapy if a response is achieved and the patient has not been previously exposed to PARPis
  - If a carboplatin-based doublet plus bevacizumab is used, PLD is preferred to gemcitabine as it has demonstrated a statistically significant PFS and overall survival advantage
- For patients requiring a rapid response, the combination of a platinum-based doublet with bevacizumab should be preferred
- Bevacizumab should be continued until disease progression (symptomatic) or until the next line of treatment is started, as continuation of bevacizumab beyond progression has not been evaluated in the recurrent setting
- PARPi therapy should be continued until disease progression or until the next line of treatment is started, as the benefit of continuing treatment beyond progression has not been demonstrated conclusively
- Platinum rechallenge following treatment with a non-platinum regimen (monotherapy or combination) could be considered if the tumour did not progress during prior platinum therapy

Non-platinum-based systemic therapy

- Patients with relapsed EOC for whom platinum is not an option should be defined by:
  - Proven resistance (progression during platinum)
  - Expected resistance (early symptomatic progression post-platinum, response to rechallenge unlikely)
  - Platinum intolerance
  - Patient choice
  - Quality of life issues
- For patients who are not candidates to receive a platinum, integrating palliative care early in the treatment pathway is strongly recommended
- Patients with a good performance status should be prioritised for novel therapies within clinical trials
  - Clinical trial participation is also strongly recommended for patients with less common histological subtypes (e.g. CCC, carcinosarcoma or LGSC) once platinum-based therapy is no longer an option
- Single-agent non-platinum options that can be recommended include weekly paclitaxel, PLD, topotecan and gemcitabine
  - The choice should be guided by patient preference and toxicity profile
  - The optimal duration of treatment is unclear
- In patients with platinum intolerance who have relapsed > 6 months after previous platinum exposure, trabectedin–PLD may be recommended [European Medicines Agency (EMA) approved, not Food and Drug Administration (FDA) approved]
- Bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and who have not been previously exposed to bevacizumab
- Hormone therapy is recommended for relapsed LGSC
- For patients with recurrent LGSC, treatment with the mitogen-activated protein kinase kinase (MEK) inhibitor, trametinib, should be considered after prior platinum-based ChT and hormone therapy (not EMA or FDA approved)

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- Although a cure is unlikely after relapse, effective therapies exist for recurrent EOC and surveillance is indicated
- Surveillance should include thorough symptom review and physical examination
  - CT scanning is indicated if symptoms suggest recurrent disease or if the CA 125 level is rising
  - However, the benefit of monitoring CA 125 levels for surveillance purposes in the current era (i.e. in the presence of more sensitive radiological detection methods and improved treatment outcomes) has yet to be defined
- Patients with *BRCA1/2*-mut tumours can be considered for follow-up beyond 5 years, with long-term survivors referred to high-risk breast cancer clinics for follow-up

GLOSSARY

AC, adenocarcinoma
ACE, actinomycin D–cyclophosphamide–etoposide
AFP, α-fetoprotein
AGCT, adult granulosa cell tumour
ASC, adenosquamous carcinoma
ASCT, autologous stem cell transplantation
ATM, ATM serine/threonine kinase
AUC, area under the curve
BC, breast cancer
BEP, bleomycin–etoposide–cisplatin
BRIP1, BRCA1 interacting helicase 1
BSO, bilateral salpingo-oophorectomy
CA 125, cancer antigen 125
CAP, cyclophosphamide–doxorubicin–cisplatin
CBOP, carboplatin–bleomycin–vincristine–cisplatin
CC, choriocarcinoma
CCC, clear cell carcinoma
CHAMOCA, actinomycin D–cyclophosphamide–doxorubicin–melphalan–hydroxyurea–vincristine
CHEK2, checkpoint kinase 2
CHM, complete hydatidiform mole
ChT, chemotherapy
CNS, central nervous system
CO, cyclophosphamide–vincristine
CPG, Clinical Practice Guideline
CR, complete response
CRT, chemoradiotherapy
CT, computed tomography
D&C, dilation and curettage
DFS, disease-free survival
dMMR, mismatch repair deficient
EBRT, external beam radiotherapy
EC, endometrial cancer
EEC, endometrioid endometrial cancer
EGFR, epidermal growth factor receptor
EMA, European Medicines Agency
EOC, epithelial ovarian cancer
EP, etoposide–cisplatin
ESMO, European Society for Medical Oncology
ETT, epithelial trophoblastic tumour
FDA, Food and Drug Administration
FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose
FIGO, International Federation of Gynecology and Obstetrics
FOXL2, forkhead box L2
G-CSF, granulocyte colony-stimulating factor
GCT, germ cell tumour
GI, gastrointestinal
GTD, gestational trophoblastic disease
GTN, gestational trophoblastic neoplasia
HBOC, hereditary breast and ovarian cancer syndrome
hCG, human chorionic gonadotropin
HDCT, high-dose chemotherapy
HGSC, high-grade serous carcinoma
HM, hydatidiform mole
HPV, human papillomavirus
HRD, homologous recombination deficiency
HRT, hormone replacement therapy
ICS, interval cytoreductive surgery
IHC, immunohistochemistry
IP, intraperitoneal
IV, intravenous
LACC, locally advanced cervical cancer
LDH, lactate dehydrogenase
LGSC, low-grade serous carcinoma
LNE, lymphadenectomy
LVSI, lymphovascular space invasion
MAC, methotrexate–actinomycin D–cyclophosphamide
MC, mucinous carcinoma
MEK, mitogen-activated protein kinase kinase
MFA, methotrexate–folinic acid–actinomycin D
MLH1, MutL homologue 1
MMR, mismatch repair
MRI, magnetic resonance imaging
MSH2, MutS homologue 2
MSH6, MutS homologue 6
MSI-H, microsatellite instability-high
mut, mutated
mut/Mb, mutations per megabase
NACT, neoadjuvant chemotherapy
NET, neuroendocrine tumour
NSMP, no specific molecular profile
OCP, oral contraceptive pill
OCT4, octamer-binding transcription factor 4
OS, overall survival
p53, tumour protein p53

GLOSSARY (CONT'D)

p53-abn, p53-abnormal
PALB2, partner and localiser of *BRCA2*
PARPi, poly (ADP-ribose) polymerase inhibitor
PCS, primary cytoreductive surgery
PD, pulmonary disease
PET, positron emission tomography
PFS, progression-free survival
PGT, preimplantation genetic testing
PHM, partial hydatidiform mole
PLD, pegylated liposomal doxorubicin
PLND, pelvic lymph node dissection
PMS2, PMS1 homologue 2
POLE, polymerase epsilon
*POLE*mut, polymerase epsilon-ultramutated
POMB, cisplatin–vincristine–methotrexate–bleomycin
PRS, polygenic risk score
PS, performance status
PSTT, placental site trophoblastic tumour
PV, pathogenic variant
PVB, cisplatin–vinblastine–bleomycin
QoL, quality of life
RAD51C, RAD51 paralogue C
RAD51D, RAD51 paralogue D
RRBSO, risk-reducing bilateral salpingo oophorectomy
RT, radiotherapy
SALL4, spalt-like transcription factor 4
SCC, squamous cell carcinoma
SCCOHT, small cell carcinoma of the ovary hypercalcaemic type
SCNA, somatic copy number alteration
SCST, sex cord stromal tumour
SEE-FIM, Sectioning and Extensively Examining the FIMbriated End
SLCT, Sertoli-Leydig cell tumour
SLN, sentinel lymph node
SLND, sentinel lymph node dissection
SMARCA4, SWI/SNF-related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SNP, single nucleotide polymorphism
SoC, standard of care
SOX2, sex-determining region Y-box transcription factor 2
TC, carboplatin–paclitaxel
TCGA, The Cancer Genome Atlas
TE, paclitaxel–etoposide
TNM, tumour–node–metastasis
TP, paclitaxel–cisplatin
TP53, tumour suppressor protein p53
TVUS, transvaginal ultrasound
UICC, Union for International Cancer Control
UK, United Kingdom
US, ultrasound
VAC, vincristine–actinomycin D–cyclophosphamide
VBT, vaginal brachytherapy
VeIP, vinblastine–ifosfamide–cisplatin
WHO, World Health Organization
WT, wild type
YST, yolk sac tumour

NOTES

NOTES

Access the full ESMO Clinical Practice Guidelines

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