ESGO

Pocket Guidelines

Management of Patients with **Endometrial Carcinoma**

THE EUROPEAN VOICE OF GYNAECOLOGICAL ONCOLOGY

Pocket Guidelines

Based on ESGO-ESTRO-ESP guidelines for the management of patients with endometrial carcinoma: update 2025

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ESGO

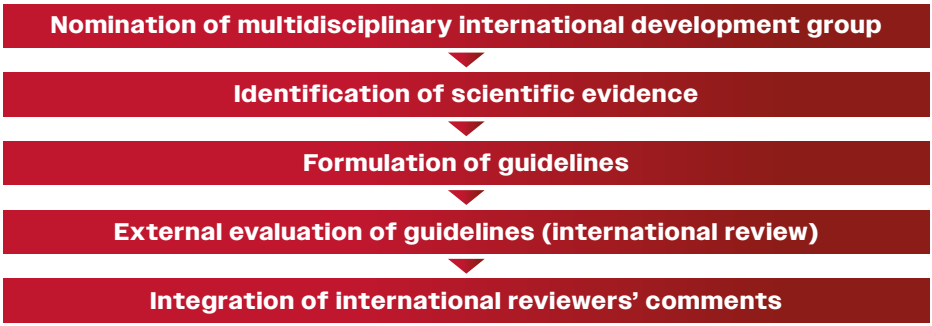
The European Society of Gynaecological Oncology (ESGO), the European Society of Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) developed and published guidelines for the management of patients with endometrial carcinoma in 2021.

In 2023, the International Federation of Gynaecology and Obstetrics (FIGO) staging system was updated due to advances in the understanding of the pathological and molecular features of endometrial carcinoma. The update aimed to more precisely define prognostic groups and identify relevant treatment subgroups by including factors that reflect tumour biology (histological subtypes, lymphovascular space invasion (LVSI), and molecular classification) and refinements of anatomical factors (peritoneal carcinomatosis and lymph node metastasis).

As part of its mission to improve the quality of care for people with gynaecological cancers, ESGO, ESTRO, and ESP have now updated these joint evidence-based guidelines in endometrial carcinoma and added new topics to cover comprehensive diagnosis, management, follow-up, and patient education. These updated guidelines consider the large body of new evidence in this field and incorporate the revised 2023 FIGO staging, which reflects the improved understanding of the complex nature of the different types of endometrial carcinoma and their underlying biological behaviour. Fertility-sparing treatment in patients with endometrial carcinoma is covered by the evidence-based guidelines developed jointly by ESGO, the European Society of Human Reproduction and Embryology, and the European Society for Gynaecological Endoscopy published in 2023, and thus was not included in these guidelines.

For simplification, and to facilitate easy reading, mismatch repair deficient (MMRd) is used as a synonym for MMRd or microsatellite instable throughout the document. Furthermore, we use non-MMRd instead of mismatch repair proficient, underpinning the fact that mismatch repair proficient does not reflect a molecularly defined, homogeneous group of patients with endometrial carcinoma. Non-MMRd is used as a synonym for mismatch repair proficient or microsatellite stable throughout the document.

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee:



The objectives of these ESGO-ESTRO-ESP guidelines are to improve the quality of care for patients with endometrial carcinoma across Europe and worldwide. They are intended for use by all health professionals involved in the management of these patients across all allied disciplines.

These guidelines do not include any economic analysis of the strategies. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A literature review of relevant studies published between June 2019 and October 2023 was carried out. In addition, available data of randomised controlled trials published between October 2023 and January 2025 were considered.

The guidelines were adopted if they were supported by sufficient high level of scientific evidence and/or when a large consensus among experts was obtained. An adapted version of the "Infectious Diseases Society of America-United States Public Health Service Grading System" was used to define the level of evidence and grade of recommendation for each of the recommendations:

LEVELS OF EVIDENCE

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

GRADES OF RECOMMENDATIONS

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

ESGO would like to thank the members of the international development group for their constant availability, work, and for making possible the development of these guidelines for the management of patients with endometrial carcinoma (see below). ESGO is also very grateful to the 228 international external reviewers (clinicians and patient representatives) for their participation (list available on the ESGO website).

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General recommendations

A Planning of staging and treatment should be made in a multidisciplinary setting (generally at a tumour board meeting composed according to local guidelines) and based on the comprehensive and precise knowledge of prognostic and predictive factors for outcome, morbidity, and quality of life.

A Patients should be carefully counselled about the suggested diagnostic and treatment plans and potential alternatives, including risks and benefits of all options.

A Treatment should be undertaken in a specialised centre by a dedicated team of specialists in the diagnosis and management of gynaecological cancers, especially in high-risk disease, advanced stage disease, or both.

Lynch identification and surveillance

A To identify patients with a higher risk of Lynch syndrome and to triage for germline mutational analysis (prescreening), immunohistochemistry for mismatch repair proteins (plus analysis of MLH1 promotor methylation status in cases of immunohistochemistry loss of MLH1 alone or MLH1 plus PMS2 expression) is the preferred option and should be done for all patients with endometrial carcinoma.

B Microsatellite instability testing is a secondary option to pre-screening for Lynch syndrome.

B Patients with endometrial carcinoma identified as having an increased risk of Lynch syndrome by mismatch repair immunohistochemistry (with or without MLH1 methylation analysis) or microsatellite instability testing, or family history, should be offered genetic counselling, including genetic testing and surveillance of related cancers.

B Surveillance for endometrial carcinoma in carriers of Lynch syndrome mutations should generally start at age 30 years; however, individual factors must be considered (tailored surveillance programmes). The decision on the starting age of surveillance should integrate knowledge on the specific mutation and history of onset of events in the family.

B Surveillance of the endometrium with annual transvaginal ultrasound and annual or biennial biopsy until hysterectomy should be considered in all carriers of Lynch syndrome mutations.

B Hysterectomy and bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer by minimally invasive surgery should be offered once the patient has decided not to have children or further children (ie, completed family planning) and preferably before age 40 years in patients with MLH1, MSH2, or MSH6 mutations. Hysterectomy and bilateral salpingo-oophorectomy are recommended at the time of menopause in patients with PMS2 mutations. The advantages and disadvantages of prophylactic surgery must be discussed, including the risk of occult gynaecological cancer detection during surgery. Oestrogen replacement therapy should be suggested after bilateral salpingo-oophorectomy in premenopausal women.

Integration of molecular classification and other biomarkers

A Molecular classification (*POLE*-mutated [*POLE*mut], mismatch repair deficient [MMRd], no specific molecular profile [NSMP], or p53-abnormal [p53abn] endometrial carcinomas) should be done for all types of endometrial carcinoma and requires three basic analyses (2020 WHO tumour classification.

B Molecular classification is particularly relevant in high-grade carcinomas.

C *POLE* analysis might be omitted in low-risk, stage I endometrial carcinoma in which *POLE* mutational status does not influence adjuvant treatment decision making.

B Molecular testing is encouraged on endometrial biopsy or curettage material. It needs to be repeated on the hysterectomy specimen only in specific situations, including scant tumour tissue, equivocal results, or technical problems on biopsy, or in the presence of an additional tumour component in the hysterectomy specimen that was not present in the biopsy.

B Mismatch repair testing should be done by immunohistochemistry. The two-antibody approach is equivalent to the four-antibody approach.

B In case of equivocal or heterogeneous mismatch repair immunohistochemistry results, it should be supplemented by microsatellite PCR.

B For p53 status testing, immunohistochemistry is recommended. *TP53* mutational analysis is a good alternative to p53 testing by immunohistochemistry and should be used when immunohistochemistry is equivocal or heterogeneous.

B *POLE* mutational status testing should cover all 11 pathogenic *POLE* exonuclease domain variants.

B Endometrial carcinoma with multiple classifier features should be classified according to their genomic driver, such as a pathogenic *POLE* mutation (combination of *POLE*mut with p53abn or MMRd, or both) or mismatch repair deficiency (combination of MMRd with p53abn).

A It is recommended to test oestrogen receptor status by immunohistochemistry in all endometrial carcinomas because it can facilitate diagnosis, is prognostic in the NSMP group, and is predictive for response to endocrine therapy in advanced and recurrent disease.

C All advanced and recurrent p53abn endometrial carcinomas and all serous carcinomas or carcinosarcomas might be tested for HER2 (also known as ERBB2) overexpression by immunohistochemistry and, in case of an immunoreactive score of 2+, by in situ hybridisation using standardised criteria.

A The development of molecularly driven and biomarker-driven clinical trials are recommended to further strive towards precision medicine in the management of patients with endometrial carcinoma.

Definition of risk groups

Figures 1 and 2 depict an integrated approach towards prognostic risk group allocation based on either the FIGO 2023 staging system with known molecular classification or on tumour extension, LVSI status, and known molecular classification (depicting the corresponding FIGO 2023 stages).

Prognostic risks are defined as estimated overall 5-year risk of recurrence in the low-risk group (<8%), intermediate-risk group (8-14%), high–intermediate-risk group (15–24%), and high-risk group (≥25%).

Allocation to a prognostic risk group without knowledge of molecular classification is provided in the appendix of the article. Of note, particularly in high-grade histologies, molecular classification is needed to allow proper risk group allocation.

Figure 1 - Definition of risk groups based on FIGO 2023 staging and molecular classification

2023 FIGO staging*			Molecular classification				
			*POLE*mut	MMRd	NSMP low-grade and ER-positive	NSMP high-grade or ER-negative (or both)‡	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, confined to polyp or endometrium (no myoinvasion)	IAm *POLE*mut			‡	
	IA2	Low-grade endometrioid, myoinvasion <50%, no or focal LVSI	IAm *POLE*mut			‡	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium and ovary§				‡	
IB		Low-grade endometrioid, myoinvasion ≥50%, no or focal LVSI	IAm *POLE*mut			‡	IICm p53abn
IC		High-grade histologies¶, limited to polyp or endometrium	IAm *POLE*mut		NA		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			‡	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI‖	IAm *POLE*mut			‡	IICm p53abn
IIC		High-grade histologies¶, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no or focal LVSI	NA		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no or focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no or focal LVSI			
			IAm *POLE*mut	Substantial LVSI‖			
III	**Local spread, regional spread, or both**						
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina, parametria, or both					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV	**Locally advanced disease, metastatic disease, or both**						
IVA		Invasion of bladder mucosa or intestinal mucosa, or both					
	Metastatic disease or residual disease after surgery						
III or IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Green denotes low risk of recurrence, yellow denotes intermediate risk, orange denotes high–intermediate risk, red denotes high risk, and grey denotes uncertain risk classification because of insufficient data. ER=oestrogen receptor. FIGO=International Federation of Gynaecology and Obstetrics. m=molecular. LVSI=lymphovascular space invasion. MMRd=mismatch repair deficient. NA=not applicable. NSMP=no specific molecular profile. p53abn=abnormal p53. *POLE*mut=*POLE* mutant. pT1a=unilateral ovarian tumour confined to the ovary without capsule invasion or breach. *When molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular), followed by the specific molecular subtype. There are two specific, molecularly defined FIGO stages: IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion). ‡The molecular subgroup NSMP high-grade or ER-negative (or both) consists of either high-grade NSMP endometrial carcinoma, or ER-negative NSMP endometrial carcinoma, or of NSMP endometrial carcinomas with a combination of both high grade and ER negativity. Thus, in FIGO stages referring to low-grade endometrioid carcinomas (ie, IA1, IA2, IA3, IB, IIA, and IIB) only the ER-negative cases apply in the molecular subgroup NSMP high-grade or ER-negative (or both). §Myoinvasion less than 50% and no LVSI and ovarian tumour pT1a. ¶High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3); serous, clear cell carcinomas; carcinosarcomas; and undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma. ‖Substantial LVSI is defined according to WHO criteria in at least one haematoxylin and eosin-based staining slide.

Figure 2 - Definition of risk groups based on anatomic tumour extent, LVSI status, and molecular classification, showing corresponding FIGO 2023 stages

	Molecular classification				
	*POLE*mut	MMRd	NSMP low-grade and ER-positive	NSMP high-grade or ER-negative (or both)†	p53abn
Confined to the uterine corpus					
No myoinvasion, confined to polyp or endometrium	IAm *POLE*mut	IA1 or IC‡	IA1	IA1 or IC‡	IA1 or IC‡
Myoinvasion <50%, no or focal LVSI	IAm *POLE*mut	IA2 / IIC‡	IA1	IA2 or IIC‡	IICm p53abn
Myoinvasion ≥50%, no or focal LVSI	IAm *POLE*mut	IB or IIC‡	IB	IB or IIC‡	IICm p53abn
Confined to the uterus (uterine corpus with or without cervical invasion)					
Cervical stromal invasion, no or focal LVSI	IAm *POLE*mut	IIA or IIC‡	IIA	IIA or IIC‡	IICm p53abn
Uterine corpus with or without cervical invasion, substantial LVSI§	IAm *POLE*mut	IIB or IIC‡	IIB	IIB or IIC‡	IICm p53abn
Local spread, regional spread, or both					
Spread to ovary or fallopian tube¶	IIIA1	IIIA1	IIIA1	IIIA1	IIIA1
Involvement of uterine subserosa or spread through the uterine serosa	IIIA2	IIIA2	IIIA2	IIIA2	IIIA2
Metastasis or direct spread to the vagina, parametrium, or both	IIIB	IIIB	IIIB	IIIB	IIIB
Metastasis to the pelvic peritoneum	IIIB2	IIIB2	IIIB2	IIIB2	IIIB2
Metastasis to the pelvic lymph nodes	IIIC1	IIIC1	IIIC1	IIIC1	IIIC1
Metastasis to the para-aortic lymph nodes	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2
Locally advanced					
Invasion of bladder mucosa, intestinal mucosa, or both	IVA	IVA	IVA	IVA	IVA
Low-grade endometrioid carcinoma of both the endometrium and ovary					
Myoinvasive <50%, no LVSI, ovarian tumour pT1a	IA3	IA3	IA3	IA3†	IA3
Metastatic or residual disease after surgery					
Local spread, regional spread, or both with residual disease	III with residual disease				
Invasion of bladder mucosa, intestinal mucosa, or both with residual disease	IVA with residual disease				
Peritoneal metastasis beyond pelvis	IVB				
Distant metastasis	IVC				

Green denotes low risk of recurrence, yellow denotes intermediate risk, orange denotes high–intermediate risk, red denotes high risk, and grey denotes uncertain risk classification because of insufficient data. When molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific, molecularly defined FIGO stages: stage IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion). ER=oestrogen receptor. FIGO=International Federation of Gynaecology and Obstetrics. LVSI= lymphovascular space invasion. m=molecular. MMRd=mismatch repair deficient. NA=not applicable. NSMP=no specific molecular profile. p53abn=abnormal p53. *POLE*mut=*POLE* mutant. pT1a=unilateral ovarian tumour confined to the ovary without capsule invasion or breach. †The molecular subgroup NSMP high-grade or oestrogen receptor-negative (or both) consists of either high-grade NSMP endometrial carcinoma, or oestrogen receptor-negative NSMP endometrial carcinoma, or of NSMP endometrial carcinomas with a combination of both high grade and oestrogen-receptor negativity. Thus, in low-grade endometrioid carcinomas of both the endometrium and ovary, only the oestrogen receptor-negative cases apply in the molecular subgroup NSMP high-grade or oestrogen receptor-negative (or both). ‡High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3); serous, clear cell carcinomas; carcinosarcomas; and undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma. §Substantial LVSI is defined according to WHO criteria in at least one haematoxylin and eosin-based staining slide. ¶Except for low-grade endometrioid carcinoma of both the endometrium and ovary with myoinvasion less than 50% and no LVSI and ovarian tumour pT1a.

Early-stage disease

Surgical management in presumed stage I and II disease

Standard surgical procedures

A (stage I) **B** (stage II) Standard surgery for stage I and II endometrial carcinoma is total hysterectomy with bilateral salpingo-oophorectomy and lymph node staging.

B Infracolic (total or partial) omentectomy should be done for clinical stage I and II serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma. Omentectomy is not necessary in other histological types.

B For patients with stage II disease and cervical involvement, more extensive procedures should only be done if required to achieve free surgical margins.

Minimally invasive approach

A Minimally invasive surgery is the preferred surgical approach, including for patients with high-risk endometrial carcinoma.

A Any intraperitoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided.

B If vaginal extraction risks uterine rupture, other measures should be taken (eg, mini-laparotomy or use of endobag).

B A preoperative or intraoperative finding of metastatic spread outside the uterus (excluding lymph node metastases) is a relative contraindication for minimally invasive surgery.

Lymph node staging

A Sentinel lymph node biopsy should be done for staging purposes in all patients with presumed uterus-confined disease.

A For sentinel lymph node biopsy, indocyanine green with cervical injection is the preferred detection technique. Tracer re-injection is an option if sentinel lymph nodes are not visualised upfront. If sentinel lymph nodes are not detected on either pelvic side, side-specific systematic lymphadenectomy should be done for patients at high–intermediate or high risk, and can be considered in patients at presumed intermediate risk.

A All sentinel lymph nodes should be subjected to ultrastaging (a more intensive pathological assessment of sentinel lymph nodes that can increase the accuracy of lymph node staging).

C Although in the literature, no consensus by pathologists has been reached regarding the minimal number of sectioning levels, the initial section, followed by at least two additional levels (50µ to 250µ apart combining haematoxylin and eosin-based staining and immunohistochemistry), might be a reasonable approach to combine cost-effectiveness and efficacy to detect low-volume metastasis.

C Both macrometastases and micrometastases (micrometastases defined as greater than 0·2 mm or more than 200 cells or both, but not greater than 2·0 mm, pN1[mi]) are regarded as a metastatic involvement.

C The prognostic significance of isolated tumour cells (deposits ≤ 0·2 mm; pN0[i+]) is unclear.

Ovarian preservation in stage I disease

B Ovarian preservation can be considered in premenopausal patients younger than 45 years with FIGO 2023 IA1 or IA2 who have a low risk of recurrence by molecular classification.

B In cases of ovarian preservation, bilateral salpingectomy is recommended.

B Ovaries should not be preserved in patients at hereditary risk of ovarian cancer, such as carriers of germline *BRCA* mutations or *MLH1*, *MSH2*, *MSH6*, or *PMS2* mutations (Lynch syndrome), and ovarian preservation should be carefully discussed with patients with ovarian or breast cancer family history.

Patients with stage I and II disease who are medically unfit

C Medical contraindications to the standard surgical management by minimally invasive surgery are rare. Vaginal hysterectomy with bilateral salpingo-oophorectomy, if feasible, can be considered as a curative option in patients unfit for the recommended standard surgical therapy (patients with medical comorbidities for whom standard surgery is precluded due to high operative and perioperative risks).

B Definitive curative radiotherapy is the treatment of choice in patients with a primary endometrial carcinoma diagnosis in whom standard surgery is contraindicated for medical reasons. The combination of external beam radiotherapy plus intrauterine image-guided brachytherapy should be used for high-grade tumours or deep myometrial invasion or both.

B For low-grade tumours without deep myometrial invasion, intrauterine image-guided brachytherapy alone can be considered as an alternative for the combination of external beam radiotherapy plus intrauterine image-guided brachytherapy.

B For patients who are medically unfit and are unsuitable for treatment with curative intent (standard surgery, vaginal hysterectomy, or definitive radiotherapy), systemic treatment (including endocrine therapy), a combination of local treatments (including a progestin-releasing intrauterine device and radiotherapy), or both, can be considered for palliation.

Adjuvant therapy

Adjuvant therapy guidelines for patients with endometrial carcinoma strongly depend on their prognostic risk group.

Low risk

Low risk includes four categories (figures 1, 2; green cells):

- Stages IA molecular (m; IA1, IA2, or IA3) POLEmut, MMRd, or NSMP low-grade and oestrogen receptor-positive endometrial carcinoma.
- Stage IBm POLEmut endometrial carcinoma.
- Stage ICm POLEmut or MMRd endometrial carcinoma.
- Stages IIm (IIA, IIB, or IIC) POLEmut endometrial carcinoma.

A For patients with low-risk endometrial carcinoma, no adjuvant therapy is recommended.

Intermediate risk

Intermediate risk includes three categories (figures 1, 2; yellow cells):

- Stage IBm MMRd or NSMP low-grade and oestrogen receptor-positive endometrial carcinoma.
- Stage IIAm NSMP low-grade and oestrogen receptor-positive endometrial carcinoma.
- Stage IICm MMRd endometrial carcinoma with myoinvasion (regardless of depth of myometrial invasion), without cervical stromal invasion and without substantial LVSI.

A For patients with intermediate-risk endometrial carcinoma, adjuvant vaginal brachytherapy should be considered.

C No adjuvant therapy is also an option, especially for patients younger than
A 60 years or those with low-grade endometrial carcinoma.

High-intermediate risk

High–intermediate risk includes three categories (figures 1, 2; orange cells):

- Stage IIAm MMRd endometrial carcinoma.
- Stage IIBm MMRd, or NSMP low-grade and oestrogen receptor-positive endometrial carcinoma.
- Stage IICm MMRd endometrial carcinoma with cervical invasion (independent of LVSI) or with substantial LVSI.

A For patients with high–intermediate-risk endometrial carcinoma, adjuvant external beam radiotherapy is recommended for optimal pelvic control.

B Vaginal brachytherapy is an alternative option, especially for patients who underwent lymph node staging and are pN0.

B No adjuvant therapy can be considered, especially for patients who underwent lymph node staging and are pN0 without substantial LVSI and low-grade disease.

High risk

High risk includes four categories (figures 1, 2; red cells):

- Stages IA2m, IA3m, or IBm NSMP high-grade or oestrogen receptor-negative (or both), or stages IA2m, IA3m, or IBm p53abn endometrial carcinomas.
- Stages IIm (IIA, IIB, or IIC) NSMP high-grade or oestrogen receptor-negative (or both), or p53abn endometrial carcinoma.
- Stages IIIm (IIIA, IIIB, or IIIC) MMRd, NSMP low-grade and oestrogen receptor-positive, NSMP high-grade or oestrogen receptor-negative (or both), or p53abn endometrial carcinomas.
- Stages IVAm MMRd, NSMP low-grade and oestrogen receptor-positive, NSMP high-grade or oestrogen receptor-negative (or both), or p53abn endometrial carcinomas.

A
B For patients with high-risk endometrial carcinoma, external beam radiotherapy with concurrent and adjuvant chemotherapy or, alternatively, sequential chemotherapy and radiotherapy, are recommended.

B Chemotherapy with or without brachytherapy is an alternative option.

B For patients with stage IIIm–IVAm MMRd endometrial carcinoma, adjuvant chemotherapy combined with an immune checkpoint inhibitor (with or without external beam radiotherapy) should be considered.

Uncertain risk

Uncertain risk includes two categories in early-stage disease (stages I and II) and two categories in advanced disease (stages III and IV; figures 1, 2; grey cells):

- In early-stage disease, uncertain risk categories consist of first, stage IA1m NSMP high-grade or oestrogen receptor-negative (or both), or p53abn endometrial carcinoma, and second, stage ICm NSMP high-grade or oestrogen receptor-negative (or both), or p53abn endometrial carcinoma.
- In advanced stage disease, uncertain risk categories consist of first, stage IIIm POLEmut endometrial carcinoma and second, stage IVA POLEmut endometrial carcinoma.

C In early-stage disease, there are scarce data suggesting that the risk of recurrence is somewhat higher than for low-risk carcinoma. However, adjuvant therapy is generally not recommended.

B In advanced stage disease, due to scarce data, no firm treatment guidelines can be given. However, following a case-by-case multidisciplinary team discussion, de-escalation from high-risk treatment can be considered.

Advanced disease

Surgery for clinically overt stage III and IV disease

B In patients with stage III and IV endometrial carcinoma (including carcinosarcoma), surgical cytoreduction - including resection of suspicious lymph nodes - should be considered when complete macroscopic resection is feasible with an acceptable morbidity and quality of life, following full pre-operative staging and discussion by a multidisciplinary team.

B Systematic lymphadenectomy is not recommended; only suspicious lymph nodes should be resected as part of the cytoreductive procedure.

Unresectable stage III or IV endometrial carcinoma

C For patients with unresectable stage III or IV due to local extent of disease, multidisciplinary team discussions should consider the molecular subtype of the tumour in decision making about definitive radiotherapy (with external beam radiotherapy and image-guided brachytherapy) or primary systemic treatment.

A Image-guided brachytherapy is recommended to boost uterine, parametrial, or vaginal disease.

C After a good response to primary systemic therapy, delayed surgery can be considered, depending on the suitability of the patient for surgery, the feasibility of a complete macroscopic resection, and the patient's wishes.

C If there is no indication for surgery, further systemic treatment or definitive radiotherapy (with external beam radiotherapy and image-guided brachytherapy) can be considered. Systemic therapy could be considered after definitive radiotherapy.

C Further systemic treatment or radiotherapy could be considered after surgery.

For patients with unresectable, disseminated disease or residual disease after primary surgery for stage III or IV disease, see systemic therapy section on first-line treatment.

Incomplete primary surgery

A Patients with incomplete primary surgery should be referred to a specialised centre.

No residual disease

B In presumed early-stage disease with no residual disease (based on the initial surgical report and post-surgical imaging), re-surgery should be avoided in patients with low-risk disease as defined by uterine pathological and molecular factors.

B If the patient is a candidate for surgery, the cervix should be removed. In cases of no previous lymph node staging, the sentinel lymph node should be assessed by cervical injection. If the sentinel lymph node cannot be detected, lymph node staging follows the standard principles used in primary surgery.

B Re-surgery with infracolic (total or partial) omentectomy can be considered in serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma confined to the uterus if the outcome might have an implication for adjuvant treatment strategy and after careful assessment of the morbidity of the procedure.

B As sentinel lymph node assessment cannot be done in cases of previous total hysterectomy, systematic pelvic lymphadenectomy should be considered only in patients who are not at low risk and if it can modify adjuvant treatment, since its therapeutic role has not been established.

B If the patient is undergoing re-surgery to complete staging (eg, peritoneal staging, lymph node staging, or cervix removal), retained adnexa should also be removed (except in ovarian preservation).

B The question of re-surgery only for the removal of adnexa rarely occurs and should be considered only in patients who are not low risk and after careful assessment of morbidity of the procedure.

Residual disease

Residual lymph node disease in the pelvic or para-aortic regions following surgery

A Residual lymph node disease should be evaluated for resection if the initial resection did not occur at a specialist centre.

A If the residual lymph node disease is not resectable, primary systemic therapy accounting for the molecular profile, external beam radiotherapy, or both should be used.

B External beam radiotherapy should be delivered to pelvic nodes with or without para-aortic nodes, with dose escalation to involved nodes using an integrated boost.

Residual pelvic disease (vagina, pelvic side wall, or bowel) following surgery

A Residual tumour sites should be evaluated for resection if the initial surgery did not occur at a specialist centre.

B If not operable, resectable, or both, an individualised approach with either radiotherapy or primary systemic therapy - accounting for the molecular profile - or both should be considered by a multidisciplinary team.

Recurrent disease

Locoregional recurrent disease

Radiotherapy-naive patients

A For locoregional recurrence, the preferred primary therapy should be external beam radiotherapy with or without image-guided brachytherapy and with or without chemotherapy.

A For vaginal cuff recurrence, pelvic external beam radiotherapy plus intracavitary image-guided brachytherapy (with or without interstitial image-guided brachytherapy) is recommended.

A In cases of superficial tumours, intracavitary image-guided brachytherapy alone can be considered.

C An easily accessible, superficial vaginal tumour can be resected vaginally before radiotherapy.

Radiotherapy-pretreated patients

C After previous adjuvant brachytherapy only, an external beam radiotherapy and image-guided brachytherapy boost is recommended.

A After previous external beam radiotherapy (with or without brachytherapy), the molecular subtype should be considered in the decision making about radical surgery or chemotherapy and immune checkpoint inhibitors, followed by immune checkpoint inhibitors in patients with MMRd tumours who are immune checkpoint inhibitor-naive.

B

A Radical surgery should only be done if complete resection with clear margins in a curative intent seems feasible with acceptable morbidity.

B If radical surgery is not feasible, primary systemic therapy should be considered, considering the molecular profile.

C Delayed surgery after initial systemic therapy could be considered depending on response.

C Re-irradiation with curative intent could be considered in a specialised centre for patients with previous external beam radiotherapy for whom surgery is not feasible.

Oligometastatic recurrent disease

B Patients with oligometastatic disease (between one and five metastases in up to three regions) should be considered for local therapy. Treatment options include surgery, radical radiotherapy - including stereotactic radiotherapy - and local ablating techniques.

C Following local treatment, systemic therapy could be considered.

Disseminated recurrent disease

B In recurrent disseminated disease (including peritoneal and lymph node relapse), surgery should only be considered if complete macroscopic resection is feasible with acceptable morbidity and quality of life. Systemic therapy or radiotherapy should be considered postoperatively, depending on the extent and pattern of relapse and the amount of residual disease.

B If surgery is not feasible, systemic therapy should be considered. Palliative surgery can be done in selected cases to alleviate symptoms (eg, bleeding, fistula, or bowel obstruction).

A Palliative radiotherapy is indicated for symptoms related to pelvic or systemic disease.

Systemic therapy

First-line systemic therapy in unresectable stage III/IV or recurrent endometrial carcinoma with no previous chemotherapy, except in the adjuvant setting (including patients with residual disease after surgery)

A Mismatch repair status should be considered to establish the choice of first-line therapy. Patients with MMRd tumours should be offered an immune checkpoint inhibitor (eg, dostarlimab, durvalumab, or pembrolizumab) in combination with carboplatin - paclitaxel chemotherapy, followed by immune checkpoint inhibitors as maintenance therapy.

A Patients with non-MMRd tumours with rapidly growing or symptomatic disease should be offered carboplatin - paclitaxel chemotherapy.

B Immune checkpoint inhibitors plus chemotherapy, followed by immune checkpoint inhibitors as maintenance therapy (eg, dostarlimab or pembrolizumab), or immune checkpoint inhibitors plus chemotherapy, followed by immune checkpoint inhibitors and PARP inhibitors as maintenance therapy (eg, durvalumab and olaparib), can be considered.

C If chemotherapy is contraindicated in patients with non-MMRd relapsed disease and previous chemotherapy in the adjuvant or neoadjuvant setting, pembrolizumab plus lenvatinib can be considered.

B If immune checkpoint inhibitors (with or without PARP inhibitors) are contraindicated for patients with a HER2 3+ (strong overexpression) tumour, carboplatin–paclitaxel plus trastuzumab can be considered.

A The standard chemotherapy regimen is six cycles of carboplatin–paclitaxel.

A In low-grade oestrogen receptor-positive, low volume or asymptomatic, advanced or slowly growing recurrent tumours, endocrine therapy is the preferred systemic therapy. In these instances, progestins (medroxyprogesterone or megestrol) are recommended.

C Alternatives include aromatase inhibitors and tamoxifen.

B Surgery or definitive external beam radiotherapy with or without brachytherapy could be considered in patients responding to systemic treatments.

Second-line systemic therapy in unresectable recurrent disease after first-line platinum-based chemotherapy

B Patients who have not received immune checkpoint inhibitors as part of first-line therapy should be considered for immune checkpoint inhibitors as second-line treatments. Treatment should be based on mismatch repair status. If feasible, repeated mismatch repair testing should be considered on a relapsed tissue sample to guide treatment.

A For immune checkpoint inhibitor-naive patients with MMRd tumours, the preferred option should be an immune checkpoint inhibitor monotherapy, such as dostarlimab or pembrolizumab.

B Pembrolizumab plus lenvatinib could be considered.

A Immune checkpoint inhibitor-naive patients with non-MMRd tumours should be offered pembrolizumab and lenvatinib.

B For immune checkpoint inhibitor-naive patients with non-MMRd tumours for whom pembrolizumab and lenvatinib is not suitable, there is no standard systemic therapy. Platinum combination, doxorubicin, weekly paclitaxel, or endocrine therapy could be offered.

B For patients with HER2 overexpressing tumours, HER2 targeting strategies could be considered.

B Patients who have received immune checkpoint inhibitors as part of first-line therapy should be considered for systemic therapy with a platinum combination, doxorubicin, weekly paclitaxel, or endocrine therapy.

B For patients with HER2 overexpressing tumours, HER2 targeting strategies could be considered.

Further lines of systemic therapy

B The use of multiple lines of systemic therapy, particularly in platinum-pretreated and immune checkpoint inhibitor-pretreated patients, should be carefully evaluated for individuals, considering the low efficacy and weighed against best supportive care.

Follow-up

A Patients with endometrial carcinoma should be actively informed and counselled about their follow-up (including programmes for long-term survivorship).

A Patients should be informed about the signs and symptoms of endometrial carcinoma recurrence and long-term side-effects of medical interventions.

A Patients with endometrial carcinoma should be informed that the primary objectives of follow-up include psychosocial assistance and the detection of health problems, but that there is no evidence that follow-up visits improve overall survival.

A A personalised follow-up approach to individual factors, such as prognostic factors (eg, molecular classification), applied treatment modalities, potential acute and long-term side-effects, comorbidities, and the patients' needs is recommended.

A Follow-up should include assessment of physical (eg, cardiovascular comorbidities and secondary cancers) and mental health.

Patient education and empowerment of patients

B	Physicians are encouraged to empower patients to participate actively in self-decision making and self-management.
A	Patients should be informed about specialised centres and the possibility to enrol in clinical trials.
A	Cancer screening, medical follow-up, and vaccination programmes according to local guidelines should be recommended to all patients.
A	Lifestyle counselling in physical activity, a well-balanced diet, healthy weight, and smoking cessation should be routinely offered.
A	Access to psycho-oncological support and patient advocacy groups should be made available.
A	Quality of life, sexual health, menopause management, and side-effects of therapy should be repeatedly addressed.

Access the full ESGO Guidelines

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