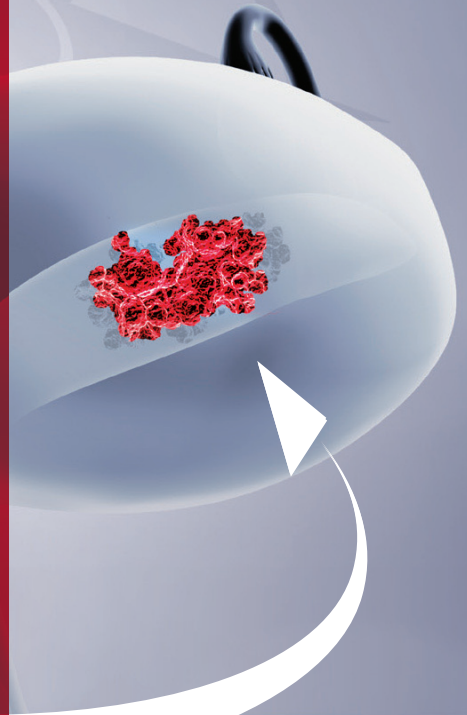


**ENDOMETRIAL
CANCER
POCKET
GUIDELINES**



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POCKET GUIDELINES

Based on

**ESGO-ESTRO-ESP guidelines
for the management of patients
with endometrial carcinoma**

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A European consensus conference on endometrial carcinoma was held in 2014 to produce multi-disciplinary evidence-based guidelines on 12 selected questions. Given the large body of literature on the management of endometrial carcinoma published since 2014, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly decided to update these evidence-based guidelines and to cover new topics in order to provide comprehensive guidelines on all relevant issues of diagnosis and treatment in endometrial carcinoma in a multi-disciplinary setting.

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 women with endometrial carcinoma across Europe and worldwide. They are intended for use by gynecological oncologists, general gynecologists, surgeons, radiation oncologists, pathologists, medical and clinical oncologists, radiologists, general practitioners, palliative care teams, and allied health professionals.

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 systematic literature review of relevant studies published between January 2014 and June 2019 was carried out.

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 a control group, case reports, and/or 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

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General recommendations

- A** Planning of staging and treatment should be made on a multi-disciplinary basis (generally at a tumor 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 counseled about the suggested diagnostic and treatment plan and potential alternatives, including risks and benefits of all options.
- A** Treatment should be undertaken in a specialized center by a dedicated team of specialists in the diagnosis and management of gynecological cancers, especially in high-risk and/or advanced stage disease.

Identification and surveillance of women with a pathogenic germline variant in a Lynch syndrome-associated gene

- B** To identify patients with Lynch syndrome and triage for germline mutational analysis, MMR IHC (plus analysis of *MLH1* promotor methylation status in case of immunohistochemical loss of MLH1/PMS2 expression) or MSI tests should be performed in all endometrial carcinomas, irrespective of histologic subtype of the tumor.
- B** Endometrial carcinoma patients identified as having an increased risk of Lynch syndrome should be offered genetic counseling.
- B** Surveillance for endometrial carcinoma in Lynch syndrome mutation carriers should in general start at the age of 35 years; however, individual factors need to be taken into consideration (tailored surveillance programs). 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 by annual transvaginal ultrasound (TVUS) and annual or biennial biopsy until hysterectomy should be considered in all Lynch syndrome mutation carriers.
- B** Hysterectomy and bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer should be performed at the completion of childbearing and preferably before the age of 40 years. All the pros and cons of prophylactic surgery must be discussed including the risk of occult gynecological cancer detection at prophylactic surgery. Estrogen replacement therapy should be suggested if bilateral salpingo-oophorectomy is performed in pre-menopausal women.

Molecular markers for endometrial carcinoma diagnosis and as determinants for treatment decisions

- B** Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors.
- C** POLE mutation analysis may be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology.

Definition of prognostic risk groups integrating molecular markers

- B** Histopathologic type, grade, myometrial invasion, and LVSI (no/focal/substantial) should be recorded in all patients with endometrial carcinoma.

The definition of prognostic risk groups for both situations when molecular classification is known or unknown is presented as follows:

Risk Group	Molecular Classification Unknown	Molecular Classification Known ^{A,*}
Low	<ul style="list-style-type: none"> • Stage IA endometrioid + low-grade** + LVSI negative or focal 	<ul style="list-style-type: none"> • Stage I-II POLEmut endometrioid carcinoma, no residual disease • Stage IA MMRd/NSMP endometrioid carcinoma + low-grade** + LVSI negative or focal
Intermediate	<ul style="list-style-type: none"> • Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion 	<ul style="list-style-type: none"> • Stage IB MMRd/NSMP endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA MMRd/NSMP endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA p53abn and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	<ul style="list-style-type: none"> • Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II 	<ul style="list-style-type: none"> • Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB MMRd/NSMP endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II MMRd/NSMP endometrioid carcinoma
High	<ul style="list-style-type: none"> • Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease 	<ul style="list-style-type: none"> • Stage III-IVA MMRd/NSMP endometrioid carcinoma with no residual disease • Stage I-IVA p53abn endometrioid carcinoma with myometrial invasion, with no residual disease • Stage I-IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	<ul style="list-style-type: none"> • Stage III-IVA with residual disease • Stage IVB 	<ul style="list-style-type: none"> • Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

^AFor stage III-IVA **POLEmut** endometrioid carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both **POLEmut** and **p53abn** should be managed as **POLEmut**)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, **POLEmut**: polymerase ϵ mutated

Pre- and intra-operative work-up

- A** Histopathologic tumor type and grade in endometrial biopsy is required.
- C** Pre-operative mandatory work-up includes: family history; general assessment and inventory of co-morbidities; geriatric assessment, if appropriate; clinical examination, including pelvic examination; expert transvaginal or transrectal ultrasound or pelvic MRI.
- C** Depending on clinical and pathologic risk, additional imaging modalities (thoracic, abdominal and pelvic CT scan, MRI, PET scan, or ultrasound) should be considered to assess ovarian, nodal, peritoneal, and other sites of metastatic disease.
- A** Intra-operative frozen section is not encouraged for myometrial invasion assessment because of poor reproducibility and interference with adequate pathologic processing.

Early stage disease

Surgical management of apparent stage I/II endometrial carcinomas

- A** **Minimally invasive approach**
Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma.
- B** Any intra-peritoneal tumor spillage, including tumor 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, use of endobag).
- B** Tumors with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications for minimally invasive surgery.

Standard surgical procedures

- A** Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff resection.
- B** Staging infracolic omentectomy should be performed in clinical stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma. It can be omitted in clear cell and endometrioid carcinoma in stage I disease.
- B** Surgical re-staging can be considered in previously incompletely staged patients with high- intermediate-risk/ high-risk disease if the outcome might have an implication for adjuvant treatment strategy.

Lymph node staging

A Sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group.

B Surgical lymph node staging should be performed in patients with high-intermediate-risk/high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II.

If sentinel lymph node biopsy is performed:

- A**
 - Indocyanine green with cervical injection is the preferred detection technique.
 - Tracer re-injection is an option if sentinel lymph node is not visualized upfront.
 - Side-specific systematic lymphadenectomy should be performed in high-intermediate-risk/high-risk patients if sentinel lymph node is not detected on either pelvic side.
 - Pathologic ultrastaging of sentinel lymph nodes is recommended.

B When a systematic lymphadenectomy is performed, pelvic and para-aortic infrarenal lymph node dissection is suggested.

C Presence of both macrometastases and micrometastases (<2 mm, pN1(mi)) is regarded as a metastatic involvement.

C The prognostic significance of ITCs, pNO(i+), is still uncertain.

B If pelvic lymph node involvement is found intra-operatively, further systematic pelvic lymph node dissection should be omitted. However, debulking of enlarged lymph nodes and para-aortic staging can be considered.

Option for ovarian preservation and salpingectomy in stage III

A Ovarian preservation can be considered in pre-menopausal patients aged <45 years with low-grade endometrioid endometrial carcinoma with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease.

B In cases of ovarian preservation, salpingectomy is recommended.

B Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (eg, *BRCA* mutation, Lynch syndrome, etc).

B

Radicality of surgery for clinical stage II

Total hysterectomy with bilateral salpingo-oophorectomy and lymph node staging is the surgical standard of care in patients with stage II endometrial carcinoma.

B

More extensive procedures should only be performed if required to achieve free surgical margins.

C

Medically unfit patients

Medical contra-indications to the standard surgical management by minimally invasive surgery are rare. Vaginal hysterectomy, with bilateral salpingo-oophorectomy if feasible, can be considered in patients unfit for the recommended standard surgical therapy.

B

Definitive radiotherapy can be considered for primary tumors where surgery is contra-indicated for medical reasons:

- The combination of EBRT and brachytherapy should be used for high-grade tumors and/or deep myometrial invasion.
- For low-grade tumors, brachytherapy alone can be considered.
- In medically unfit patients unsuitable for curative surgery or radiotherapy, systemic treatment (including hormonal therapy) can be considered.

Fertility preservation

A

Work-up for fertility preservation treatments

Patients who are candidates for fertility-preserving treatment must be referred to specialized centers. Fertility-sparing treatment should be considered only in patients with AH/EIN or grade 1 endometrioid endometrial carcinoma without myometrial invasion and without genetic risk factors.

A

In these patients, endometrial biopsy, preferably through hysteroscopy, must be performed.

A

AH/EIN or grade 1 endometrioid endometrial carcinoma must be confirmed/diagnosed by a pathologist experienced in gynecological pathology.

B

Radiologic imaging to assess the extension of the disease must be performed. An expert ultrasound examination can substitute pelvic MRI scan.

A

Patients must be informed that fertility-sparing treatment is not a standard treatment. Only patients who strongly desire to preserve fertility should be treated conservatively. Patients must be willing to accept close follow-up and be informed of the need for future hysterectomy in case of failure of treatment and/or after pregnancies.

C

Management and follow-up for fertility preservation

All patients should be evaluated before and after the fertility-sparing treatment at a fertility clinic.

B

Hysteroscopic resection prior to progestin therapy can be considered.

B

Medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) is the recommended treatment. Treatment with levonorgestrel intrauterine device in combination with oral progestins with or without gonadotropin-releasing hormone analogs can also be considered.

B

In order to assess response, hysteroscopic guided biopsy and imaging at 3–4 and 6 months must be performed. If no response is achieved after 6 months, standard surgical treatment is recommended.

B

Continuous hormonal treatment should be considered in responders who wish to delay pregnancy.

B

Strict surveillance is recommended every 6 months with TVUS and physical examination. During follow-up, hysteroscopic and endometrial biopsy should be performed only in case of abnormal uterine bleeding or atypical ultrasound findings.

C

Fertility-sparing treatment can be considered for intrauterine recurrences only in highly selected cases under strict surveillance.

B

Hysterectomy and bilateral salpingo-oophorectomy is recommended after childbearing due to a high recurrence rate. Preservation of the ovaries can be considered depending on age and genetic risk factors.

Synchronous presentation of low-grade endometrioid endometrial and ovarian carcinomas

B

If all WHO 2020 criteria mentioned above are met and the ovarian carcinoma is pT1a, no adjuvant treatment is recommended.

Adjuvant treatment

Low risk

- A** For patients with low-risk endometrial carcinoma, no adjuvant treatment is recommended (I, A).
- A** When molecular classification is known:
 - For patients with endometrial carcinoma stage I–II, low-risk based on pathogenic *POLE*-mutation, omission of adjuvant treatment should be considered.
 - For the rare patients with endometrial carcinoma stage III–IVA and pathogenic *POLE*-mutation, there are no outcome data with the omission of the adjuvant treatment. Prospective registration is recommended.
- C**

Intermediate risk

- A** Adjuvant brachytherapy can be recommended to decrease vaginal recurrence.
- C**
A Omission of adjuvant brachytherapy can be considered, especially for patients aged <60 years.
- When molecular classification is known, *POLE*mut and p53abn with myometrial invasion have specific recommendations (see respective recommendations for low- and high-risk).
- C** For p53abn carcinomas restricted to a polyp or without myometrial invasion, adjuvant therapy is generally not recommended.

High-intermediate risk (pN0 after lymph node staging)

- B** Adjuvant brachytherapy can be recommended to decrease vaginal recurrence.
- B** EBRT can be considered for substantial LVSI and for stage II.
- C** Adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI.
- C** Omission of any adjuvant treatment is an option.
- When molecular classification is known, *POLE*mut and p53abn have specific recommendations (see respective recommendations for low- and high-risk).

High-intermediate risk cN0/pNx (lymph node staging not performed)

- A** Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II.
- B** Additional adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI.
- B** Adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas.
- When molecular classification is known, *POLE*mut and p53abn have specific recommendations (see respective recommendations for low- and high-risk).

High risk

- A**
B EBRT with concurrent and adjuvant chemotherapy or alternatively sequential chemotherapy and radiotherapy is recommended.
- B** Chemotherapy alone is an alternative option.
- B** Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas).
- C** When the molecular classification is known, p53abn carcinomas without myometrial invasion and *POLE*mut have specific recommendations (see respective recommendations for low and intermediate-risk).

Advanced disease

Surgery for clinically overt stage III and IV disease

B

In stage III and IV endometrial carcinoma (including carcinosarcoma), surgical tumor debulking including enlarged lymph nodes should be considered when complete macroscopic resection is feasible with an acceptable morbidity and quality of life profile, following full pre-operative staging and discussion by a multi-disciplinary team.

A

Primary systemic therapy should be used if upfront surgery is not feasible or acceptable.

C

In cases of a good response to systemic therapy, delayed surgery can be considered.

B

Only enlarged lymph nodes should be resected. Systematic lymphadenectomy is not recommended.

Unresectable primary tumor due to local extent of disease

C

For unresectable tumors, multi-disciplinary team discussion should consider definitive radiotherapy with EBRT and intrauterine brachytherapy, or neoadjuvant chemotherapy prior to surgical resection or definitive radiotherapy, depending on response.

A

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

B

Chemotherapy should be considered after definitive radiotherapy.

Residual pelvic or para-aortic lymph nodes following surgery

B

Residual lymph node disease should be treated with a combination of chemotherapy and EBRT or chemotherapy alone.

B

EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost.

Residual pelvic disease (positive resection margin, vaginal disease, pelvic side wall disease)

B

An individualized approach with either radiotherapy or chemotherapy or a combination of both modalities should be considered by a multi-disciplinary team.

Recurrent disease

Radiotherapy naïve patients

C

Patients with recurrent disease (including peritoneal and lymph node relapse) should be considered for surgery only if it is anticipated that complete removal of macroscopic disease can be achieved with acceptable morbidity. Systemic and/or radiation therapy should be considered post-operatively depending on the extent and pattern of relapse and the amount of residual disease.

B

In selected cases, palliative surgery can be performed to alleviate symptoms (eg, bleeding, fistula, bowel obstruction).

A

For locoregional recurrence, the preferred primary therapy should be EBRT ± chemotherapy with brachytherapy.

C

An easily accessible superficial vaginal tumor can be resected vaginally prior to radiotherapy.

A

For vaginal cuff recurrence:

- Pelvic EBRT + intracavitary (±interstitial) image-guided brachytherapy is recommended.
- In case of superficial tumors, intracavitary brachytherapy alone can be considered.

C

Systemic treatment can be considered before or after radiotherapy.

Radiotherapy pre-treated patients with locoregional recurrence

B

In patients with a history of previous radiation, radical surgery, including exenteration, should be considered when the intention is complete resection with clear margins.

C

Additional options to consider include intra-operative electron radiation therapy or other forms of radiation therapy.

C

If surgery is not feasible, radical re-irradiation options include stereotactic body radiotherapy targeting the recurrence, permanent seed implants, or proton therapy. In selected cases, limited volume re-irradiation with EBRT and brachytherapy boost may be an option (especially if longer interval from the first irradiation).

C

In patients who only had previous brachytherapy, EBRT + brachytherapy boost is recommended.

C

In patients where re-irradiation with EBRT is not an option, image-guided interstitial brachytherapy only is recommended (may improve outcome).

Oligometastatic recurrent disease

B

Patients with oligometastatic disease should be considered for radical local therapy.

B

Treatment options include:

- Surgery
- Radiation therapy including stereotactic radiotherapy
- Local ablating techniques

B

The additional benefit of chemotherapy is uncertain.

Systemic treatment for recurrent disease

A

Hormone therapy is the preferred front-line systemic therapy for patients with low-grade carcinomas without rapidly progressive disease.

A

Progestogens (medroxyprogesterone acetate 200 (-300) mg and megestrol acetate 160 mg) are recommended.

C

Alternative options for hormonal therapies include aromatases inhibitors, tamoxifen, fulvestrant.

A

The standard chemotherapy treatment is carboplatin AUC 5-6 + paclitaxel 175 mg/m² every 21 days for six cycles.

C

There is no standard of care for second-line chemotherapy. Doxorubicin and paclitaxel are considered the most active therapies.

C

In patients with a long platinum-free interval, re-introduction of platinum can be considered.

B

Anti-PD1-based immune therapy with pembrolizumab could be considered for second-line therapy of MSI/MMRd carcinomas. The combination of pembrolizumab and the multi-tyrosine-kinase inhibitor lenvatinib could be considered for second-line treatment of microsatellite-stable carcinomas. However, its use may be limited due to regulatory approvals or reimbursement in different countries. Clinical trial participation should be offered to all patients with relapse disease.

Palliative radiotherapy

A

Radiotherapy is indicated for palliation of symptoms related to pelvic or systemic disease.

B

Hypofractionated small volume EBRT can be used for treating primary disease in patients not fit for radical treatment.

Access full ESGO Guidelines: www.esgo.org/explore/guidelines



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