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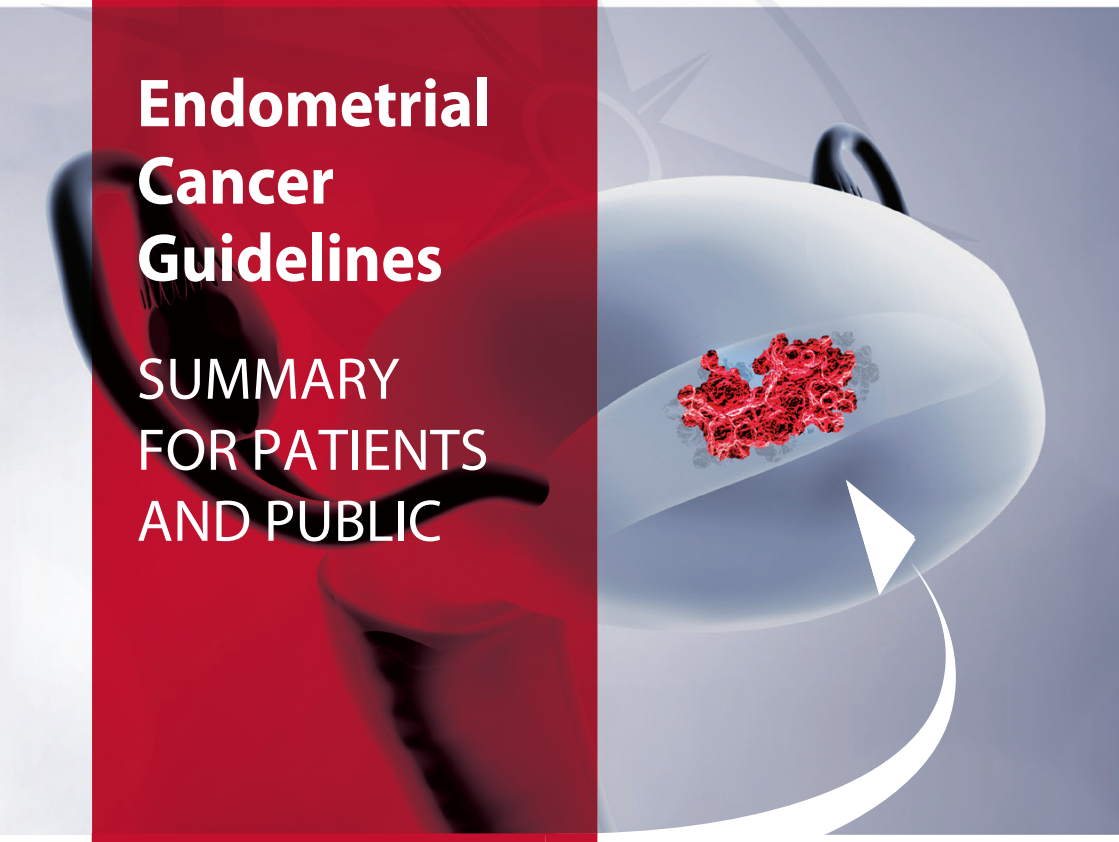
Endometrial Cancer Guidelines

SUMMARY FOR PATIENTS AND PUBLIC



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The European Society of Gynaecological Oncology (ESGO) is a non-profit organization dedicated to management and prevention of gynaecological cancer. If you wish to donate, please contact adminoffice@esgo.org. Your support will be appreciated and acknowledged.

Dear patient,

This document sets out the adapted guideline for the treatment of endometrial cancer. This is an up-to-date adaption for lay people (patients, but also a patient's relatives and friends) that has been modified from the European Society for Gynaecological Oncology (ESGO) professional guidelines that your medical team use when managing endometrial cancer.

It may be that, despite the adaptation, the technical content and terms will be difficult to understand fully. However, our aim is to show you what a professional guideline is like. Excessive simplification, which would make things look "simple", has been avoided.

We hope that after reading this guideline you will understand why your doctors ask you certain questions, administer various tests, discuss results, change decisions, and advise you to undergo or to refuse particular medical procedures. You will also see how strong and specific these recommendations sometimes are. You will see how tremendous knowledge and experience need to come together so that your medical team can foresee all the factors, including complicated ethical and psycho-social factors, needed to avoid clinical or technical errors.

On the other hand, recommendations are not always adapted to individual cases. In addition, guidelines from other international or national learned societies are available. Whatever the guidelines, your doctor is not "obliged" to follow them, but must show knowledge of them, and must explain to you the reasoning if he or she does not strictly follow them. You will see how difficult it can be sometimes to maintain an individualised, personalised attitude while simultaneously following the approved recommendations.

Finally, modern medicine is a close collaboration between doctor and patient. We must make common decisions to fight for your health, taking into account each other's opinions, experiences, feelings, and conditions. So, this adapted version of the professional guidelines is not only simple educational material about the disease but a real tool that can improve your understanding of the very serious work

Sincerely,

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The first joint European Society for Medical Oncology **(ESMO**), European Society for Radiotherapy & Oncology **(ESTRO)**, and European Society of Gynaecological Oncology **(ESGO)** consensus conference on endometrial cancer was held in December 2014 in Milan, Italy, and comprised a multidisciplinary panel of 40 leading experts in the management of endometrial cancer.

Before the conference, three clinically relevant questions were identified for each subject area/working group, giving a total of **12 clinically relevant questions** as follows:

- Which surveillance should be used for asymptomatic women?
- What work-up and management scheme should be undertaken for fertility-preserving therapy in patients with atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) and grade 1 endometrial cancer (EEC)?
- Which (molecular) markers can help distinguish (pre)cancerous lesions from benign mimics?
- How does the medical condition influence surgical treatment?
- What is the indication for lymphadenectomy; to what extent is lymphadenectomy indicated in the surgical management of endometrial cancer?
- How radical should the surgery be in different stages and pathological subtypes of endometrial cancer?
- What is the current best definition of risk groups for adjuvant therapy?
- What are the best evidence-based adjuvant treatment strategies for patients with low-and intermediate-risk endometrial cancer?
- What are the best evidence-based adjuvant treatment strategies for patients with high-risk endometrial cancer?
- Does surgery or radiotherapy (RT) have a role in advanced or recurrent endometrial cancer?
- What are the optimal systemic therapies for advanced/recurrent disease?
- What are the most promising targeted agents and which study designs should be used to evaluate their clinical benefit?

Each working group was responsible for reviewing the relevant literature in order to draft preliminary recommendations relating to each of their assigned questions. An adapted version of the Infectious Diseases Society of America-United States Public Health Service Grading System was used (Table 1) to define the level of evidence (LoE) and strength of each recommendation proposed by the group.

Finally, a vote was conducted to determine the level of agreement among the expert panel for each of the recommendations.

There are 5 levels of evidence (I–V) based on the results of scientific research:

- **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 (LoE I)
- **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 (LoE II)
- **III** Prospective cohort studies (LoE III)
- **IV** Retrospective cohort studies or case-control studies (LoE IV)
- **V** Studies without a control group, case reports, and/or expert opinions (LoE V)

Grades of recommendation

- **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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The European Network of Gynaecological Cancer Advocacy Groups (ENGAGe) is a network of European patient advocacy groups established by ESGO in 2012, representing all gynaecological cancers, particularly ovarian, endometrial, cervical, vulvar, and rare cancers.

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1. PREVENTION AND SCREENING OF ENDOMETRIAL CANCER

Which surveillance should be used for asymptomatic women?

- There is no evidence for endometrial cancer screening in the general population (LoE II) Unopposed oestrogen (hormone) treatment should not be started or should be discontinued in women with a uterus in situ (early stage, when the tumour is confined to its site of origin and has not invaded neighbouring tissue or gone elsewhere in the body) (LoE III)
- Routine surveillance in asymptomatic women with obesity, polycystic ovary syndrome, diabetes mellitus, infertility, nulliparity (a woman who has never birthed a child), or late menopause is not recommended (LoE III)
- For women with adult granulose cell tumour (tumours that arise from granulosa cells), if hysterectomy has not been performed, endometrial sampling is recommended. If this shows no evidence of (pre)malignancy, no further screening for endometrial malignancies is required (LoE IV)
- In patients with epithelial ovarian cancer (tumours involving the outer cells of the ovary/ovaries) undergoing fertility-sparing treatment, endometrial sampling is recommended at the time of diagnosis (LoE IV)
- Routine screening for endometrial cancer in asymptomatic tamoxifen (a hormonal drug that block oestrogen's effects) users is not recommended (LoE III)
- Surveillance of the endometrium by gynaecological examination, transvaginal ultrasound and aspiration biopsy (the removal of tissue or fluid with a thin needle for examination) starting from the age of 35 years (annually until hysterectomy) should be offered to all Lynch Syndrome (LS—an inherited genetic condition that increases the risk of developing some cancers) mutation carriers (LoE IV)
- Prophylactic surgery (hysterectomy and bilateral salpingo-oophorectomy), preferably using a minimally invasive approach, should be discussed at the age of 40 as an option for LS mutation carriers to prevent endometrial and ovarian cancer. All pros and cons of prophylactic surgery must be discussed (LoE IV)

What work-up and management scheme should be undertaken for fertility-preserving therapy in patients with Atypical Hyperplasia/Endometrial Intraepithelial Neoplasia (AH/EIN—a premalignant uterine lining lesion. Its presence may predispose women to endometrioid endometrial adenocarcinoma) and grade 1 endometrioid endometrial cancer (EEC)?

- Patients with AH/EIN or grade 1 EEC requesting fertility-preserving therapy must be referred to specialized centres (LoE V)
- In these patients, dilation and curettage (D&C—a procedure that takes tissue out of the uterus) with or without hysteroscopy must be performed (LoE IV)
- AH/EIN or grade 1 EEC must be confirmed/diagnosed by a specialist gynaecopathologist (LoE IV)
- Pelvic Magnetic Resonance Imaging (MRI—this uses a powerful magnetic field, radio waves, and a computer to produce pictures of the body used for diagnosis) should be performed to exclude overt myometrial invasion in and adnexal involvement. Expert ultrasound can be considered as an alternative (LoE III)
- Patients must be informed that fertility-sparing treatment is a nonstandard treatment and the pros and cons must be discussed. Patients should be willing to accept close follow-up and be informed of the need for future hysterectomy (LoE V)
- For patients undergoing fertility-preserving therapy, hormonotherapy like MPA (400–600 mg/day) or MA (160–320 mg/day) is the recommended treatment. However, treatment with other forms of progesterone, like LNG-IUD with or without Gonadotropin-releasing hormone (GnRH) analogues can also be considered (LoE IV)
- In order to assess response, D&C, hysteroscopy, and imaging at 6 months must be performed. If no response is achieved after 6 months, standard surgical treatment should be performed (LoE IV)
- In case of complete response, conception must be encouraged and referral to a fertility clinic is recommended (LoE IV)
- Maintenance treatment should be considered in responders who wish to delay pregnancy (LoE IV)
- Patients not undergoing hysterectomy should be re-evaluated clinically every 6 months (LoE IV)
- After completion of childbearing, a hysterectomy and salpingo-oophorectomy should be recommended. The preservation of the ovaries can be considered depending on age and genetic risk factors (LoE IV)

Which (molecular) markers can help distinguish (pre)cancerous lesions from benign mimics?

- In case of uncertainty, low threshold referral to a specialized gynaecopathologist is recommended (LoE V)

There are various genes responsible for controlling cells' growth, cycle, ongoing processes, and protecting from various damages and changes, that lead to cancer development. It is hard to explain to the patients the meaning of each gene/marker (PTEN, PAX-2 IHC, MLH1, ARID1, IHC, p53, ER, vimentin, CEA and p16, WT-1). But, the idea is **that these genes, their changes, mutations, and damages are used as molecular markers (diagnostic tests) that help doctors not only detect cancer, but define type, relevant treatment, and prognosis.**

For example:

- PTEN (a gene which helps prevent uncontrolled cell growth that can lead to the formation of tumours) and PAX-2 IHC are recommended to distinguish AH/EIN from benign mimics.
    - o Other markers that can be used in this context are MLH1 and ARID1a by IHC (LoE IV)
- P 53 (or TP53—a tumour protein, cellular tumour antigen which prevents cancer formation), by immunohistochemistry (IHC—the process to identify antigens (proteins) in tissue) is recommended to distinguish serous endometrial intraepithelial carcinoma (SEIC) from its mimics (LoE IV).
- Sometimes one or two markers are not enough to set diagnosis. In these cases a panel of markers is used. For example, a panel of markers must be used in cases where endocervical (relating to the endocervix—the inner, canal-like part of the cervix connecting the vagina and uterus) cancer is suspected. This panel should include at least 4 markers (ER, vimentin, CEA, and p16) by IHC and needs to be assessed in the histologic and clinical context. In addition, HPV analysis can be considered (LoE IV)
- WT-1 (Wilms tumour suppressor gene 1—a gene connected to kidney and genital abnormalities) by IHC is the recommended marker to determine the origin of serous cancer (LoE IV)
- Morphology (and not IHC) should be used to distinguish AH/EIN from EEC (LoE IV)

2. SURGERY

How does medical condition influence surgical treatment?

- Mandatory work-up must include: Family history; general assessment and inventory of comorbidities; geriatric assessment, if appropriate; clinical examination, including pelvic examination; transvaginal or transrectal ultrasound; and complete pathology assessment (histotype and grade) of an endometrial biopsy or curettage (a procedure that removes a tissue sample from the cervix using a small, spoon-shaped instrument) specimen (LoE V)
- Extent of surgery should be adapted to the medical condition of the patient (LoE V)
- In clinical stage I, grade 1 and 2: At least one of the three following tools should be used to assess myometrial invasion (which correlates with metastasis risk in the pelvic and/or paraaortic lymph nodes) if lymph node dissection (LND) is considered: Expert ultrasound and/or MRI and/or intra-operative pathological examination (LoE IV)
- Other imaging methods (thoracic, abdominal and pelvic CT scan, MRI, PET scan or ultrasound) should be considered to assess ovarian, nodal, peritoneal or metastatic disease (LoE IV)
- There is no evidence for the clinical usefulness of serum tumour markers, including CA 125 (LoE IV)
- Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff (LoE IV)
- Ovarian preservation can be considered in patients younger than 45 years old with grade 1 EEC with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease (LoE IV)
- In cases of ovarian preservation, salpingectomy is recommended (LoE IV)
- Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (e.g., BRCA mutation, LS, etc.)
- Genetic counselling/testing should be offered (LoE IV)
- Minimally invasive surgery is recommended in the surgical management of low- and intermediate-risk endometrial cancer (LoE I)
- Minimally invasive surgery can be considered in the management of high-risk endometrial cancer (LoE IV)

- Vaginal hysterectomy with salpingo-oophorectomy can be considered in patients unfit for the recommended surgery and in selected patients with low-risk endometrial cancer (LoE IV)
- In medically unfit patients, radiotherapy (RT- the treatment of disease, especially cancer, using X-rays or similar forms of radiation-ionizing radiation) or hormone treatment can be considered (LoE IV)

What are the indications for and to what extent is lymphadenectomy indicated in the surgical management of endometrial cancer

- Peritoneal cytology is no longer considered mandatory for staging (LoE IV)
- If a lymphadenectomy is performed, systematic removal of pelvic and para-aortic nodes up to the level of the renal veins should be considered (LoE IV)
- Sentinel lymph node dissection (SLND) is still experimental, but large series suggest that it is feasible. SLND increases the detection of lymph nodes with small metastases and isolated tumour cells; however, the importance of these findings is unclear (LoE IV)
- Lymphadenectomy is a staging procedure and allows tailoring of adjuvant therapy (LoE III)
- Patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, and two randomised control trials (RCTs) did not show a survival benefit. Therefore, lymphadenectomy is not recommended for these patients (LoE II)
- For patients with intermediate risk (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%), data have not shown a survival benefit. Lymphadenectomy can be considered for staging purposes in these patients (LoE II)
- For patients with high risk (grade 3 with deep myometrial invasion >50%), lymphadenectomy should be recommended (LoE IV)
- Lymphadenectomy to complete staging could be considered in previously incompletely operated high-risk patients to tailor adjuvant therapy (LoE V)

How radical should the surgery be in different stages and pathological subtypes of endometrial cancer?

- Radical hysterectomy is not recommended for the management of stage II endometrial cancer (LoE IV)
- Modified (type B-removal of the uterus, the cervix, and upper 1 cm to 2 cm of the vagina) or type A (the removal of a vaginal portion as small as possible, i.e., <10mm) radical hysterectomy should be considered only if required for obtaining free margins (LoE IV)
- Lymphadenectomy is recommended for clinical or intra-operative stage II endometrial cancer (LoE IV)
- Complete macroscopic cytoreduction (reducing the number of tumour cells by completely removing the tumour, or debulking) and comprehensive staging is recommended in advanced endometrial cancer (LoE IV)
- Multimodality management should be considered for the treatment of advanced endometrial cancer when surgery may significantly impair vaginal function (LoE IV)
- In non-EEC (apparent stage I), lymphadenectomy is recommended (LoE IV)
- Staging omentectomy (surgery to remove part or all of the omentum, the layers of peritoneum around some organs) is not mandatory in clear-cell or undifferentiated endometrial carcinoma and carcinosarcoma (LoE IV)
- Staging omentectomy should be considered in serous carcinoma (LoE IV)

What are the best evidence-based adjuvant treatment strategies for patients with low- and intermediate-risk endometrial cancer?

- In patients with low-risk endometrial cancer, no adjuvant treatment is recommended (LoE I)
- In patients with intermediate-risk endometrial cancer, adjuvant brachytherapy is recommended to decrease vaginal recurrence (LoE I)
- In patients with intermediate-risk endometrial cancer, no adjuvant treatment is an option, especially for patients aged <60 years (LoE II)
- In patients with high-intermediate risk endometrial cancer:

1. Surgical nodal staging performed, node negative:

a. Adjuvant brachytherapy is recommended to decrease vaginal recurrence (LoE III)

b. No adjuvant therapy is an option (LoE III)

2. No surgical nodal staging:

a. Adjuvant External Beam Radiation Therapy (EBRT) recommended for Lymphovascular Space Involvement (LVSI) unequivocally positive to decrease pelvic recurrence (LoE III)

b. Adjuvant brachytherapy alone is recommended for grade 3 and LVSI negative to decrease vaginal recurrence (LoE III)

3. Systemic therapy is of uncertain benefit; clinical studies are encouraged (LoE III)

3. ADVANCED AND RECURRENT ENDOMETRIAL CANCER

Does surgery or RT have a role in advanced or recurrent endometrial cancer?

- For patients with advanced or recurrent disease, surgery is recommended only if optimal cytoreduction (no residual disease) can be achieved. In selected cases, palliative surgery is recommended to alleviate specific symptoms (LoE IV)
- Exenteration (surgical removal of the contents of a bodily cavity) can be considered in selected patients with locally advanced tumours, and for isolated central local relapse after radiation, if clear margins are expected (LoE IV)
- Complete resection of distant oligometastases and pelvic or retroperitoneal lymph node relapse can be considered if technically possible according to localisation of disease (LoE V)
- Histological type should not influence the decision whether or not to proceed with surgery (LoE IV)
- RT with curative intent is indicated in patients with isolated vaginal relapse after surgery (LoE III)
- For vaginal or pelvic nodal recurrence, chemotherapy with RT could be considered in patients with high-risk features for systemic relapse (LoE IV)
- Use of systemic therapy or surgery before RT for vaginal or pelvic node recurrence could be considered in certain patients (LoE V)
- Re-irradiation could be considered in highly selected patients using specialised techniques (LoE V)
- RT is indicated for palliation of symptoms related to local recurrence or systemic disease (LoE IV). RT may be indicated for primary tumours that are unresectable, or where surgery cannot be performed or is contraindicated for medical reasons (LoE IV)

What are the optimal systemic therapies for advanced/recurrent disease

- Hormone therapy is indicated in advanced or recurrent EEC (LoE II)
- Hormone therapy is more likely to be effective in grade 1 or 2 endometrioid tumours (LoE IV)
- Hormone receptor status should be determined before hormone therapy is initiated, as it is more likely to be effective in patients with positive progesterone receptor (PgR) and oestrogen receptor (ER) status (LoE III)
- Biopsy of recurrent disease could be considered as there may be differences in hormone receptor status in the primary and metastatic tumour (LoE III)
- Hormone therapy is the preferred front-line systemic therapy for patients with hormone receptor positive tumours—grade 1 or 2 and without rapidly progressive disease (LoE V). Progestogens (e.g., MPA 200 mg or MA 160 mg) are generally recommended (LoE III)
- Other hormonal agents to consider after progestins include tamoxifen, fulvestrant, and aromatase inhibitors (LoE III)
- The standard of care is six cycles of 3-weekly carboplatin and paclitaxel (LoE I)
- There is no standard of care for second-line chemotherapy (LoE V)

What are the most promising targeted agents and which study designs should be used to evaluate their clinical benefit?

To explore the most effective targeted agents, relevant high quality and validity studies are necessary.

For example, in endometrial cancer special targeted agents (PI3K/PTEN/AKT/mTOR pathway, PTEN, RAS-MAPK, angiogenesis (especially FGFR2 and VEGF/VEGFR), ER/PgR and HRD/MSI) are altered and their relevance should be studied in clinical trials with targeted agents (LoE III).

Drugs targeting PI3K/mTOR pathway signalling and angiogenesis (PI3K signalling regulates tumour growth and angiogenesis) have shown modest activity but no agent has been approved for clinical use, and further biomarker- driven studies are warranted (LoE III)

Clinical trial designs for new, targeted therapy:

1. Basket studies with multiple cohorts related to histological subtypes and/or molecular alterations are considered a priority

2. Biomarker-driven clinical trials with biopsy at entry and sequential biopsies in trials with molecular end points are recommended

3. Progression-free survival (PFS—The length of time that a patient lives with a disease but doesn't get worse) or PFS at a defined time-point are the preferred primary end points for early phase trials

4. Overall survival (OS—The length of time that a patient survives after being diagnosed or starts treatment for a disease). In a clinical trial, measuring the OS is one way to see how well a new treatment works and is the preferred primary end point in phase III trials, unless crossover is planned or expected (LoE V)

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Access the full ESGO Guidelines

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