College of Oncology

NATIONAL EXPERT – BASED PRACTICE GUIDELINES

ENDOMETRIAL CANCER

Guidelines V1.2022

EXPERT PANEL

These guidelines have been developed by a national multi-institutional and multidisciplinary expert working party, based on international guidelines.

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INTRODUCTION

This document provides an overview of the good clinical practice guidelines for **endometrial cancer** and covers a broad range of topics such as screening, diagnosis, treatment and follow-up.

These guidelines are developed by a **panel of experts** comprising clinicians of different specialties and designated by their respective scientific societies.

The guidelines are based on the best evidence available at the time they are derived (2022).

The aim of these guidelines is to assist all national care providers involved in the care of patients with endometrial cancer and serve as a base and supporting tool for the local institutional guidelines and MOC (Multidisciplinary Oncological Consult) discussions in Belgium.

SEARCH FOR EVIDENCE

This national guideline is derived from existing international guidelines and have been updated and adapted to the Belgian context by the expert panel. The following guidelines have mostly been used: ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma (Concin et al., 2020) and the Belgian national guideline 2010. The expert panel consisted of experts in various settings and representatives of the relevant professional Belgian societies, implicated in the management of endometrial cancer.

This national guideline will be regularly updated as new evidence with practice implications emerges.

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 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.

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of other trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case report, expert opinions
Levels 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, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

LIST OF ABBREVIATIONS

AH/EIN: atypical hyperplasia/endometrioid intraepithelial neoplasia

BSO: bilateral salpingo-oophorectomy

CA125: Cancer Antigen 125

CT: computed tomography

DFS: disease-free survival

EBRT: external beam radiotherapy

EEE: ESGO/ESTRO/ESP guideline

FIGO: International Federation of Gynecology and Obstetrics

HNPCC: hereditary non-polyposis colorectal cancer

IHC: immunohistochemistry

IMRT: intensity-modulated radiation therapy

ITC: isolated tumor cells

LN: Lymph node

LVSI: lymphovascular space invasion

MMR: mismatch repair

MSH6: mutS homolog 6

MRI: Magnetic Resonance Imaging

MSI: Microsatellite instability

NGS: next generation sequencing

PET: positron emission tomography

PMS2: PMS1 homolog 2

POLE: DNA polymerase epsilon

SLN: Sentinel lymph node

TVUS: transvaginal ultra-sound

VMAT: volumetric modulated arc therapy

WG: working group

GENERAL RECOMMENDATIONS

- Planning of staging and treatment should be made on a multi-disciplinary basis (MOC) and based on prognostic and predictive factors for outcome, morbidity, and quality of life. (EEE; V, A)
- Patients should be counseled about the suggested diagnostic and treatment plan and potential alternatives, including risks and benefits of all options, including fertility-sparing treatments for young patients. (EEE + adaptation working group (WG); V, A)
- Treatment should be undertaken by a dedicated team of specialists (gynecologists/oncologists) in the diagnosis and management of gynecological cancers, especially in high-risk and/or advanced stage disease. (EEE + adaptation WG; V, A)

IDENTIFICATION AND SURVEILLANCE OF WOMEN WITH A PATHOGENIC GERMLINE VARIANT IN A LYNCH SYNDROME-ASSOCIATED GENE

- Endometrial carcinoma patients identified as having an increased risk of Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC) (MSI status, MMR IHC or familial history of HNPCC or familial endometrial cancer) should be offered genetic testing and counseling. (EEE + adaptation WG; III, B)
- Surveillance for endometrial carcinoma in Lynch syndrome mutation carriers should in general start at the age of **35** years; 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 (e.g. MSH2) and history of onset of events in the family. (EEE; IV, B)
- Surveillance of the endometrium by annual transvaginal ultra-sound (TVUS) and annual or biennial biopsy until hysterectomy should be considered in all Lynch syndrome mutation carriers starting at the age of 30 years. Furthermore, also non-endometrioid histology is possible. (EEE + adaptation WG; IV, B)
- Hysterectomy and bilateral salpingo-oophorectomy (BSO) 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 BSO is performed in pre-menopausal women. (EEE; IV, B)

Figure 1 shows the calculated complete cumulative distribution from 25 to 70 years of age for endometrial cancer. (Møller et al., 2017)

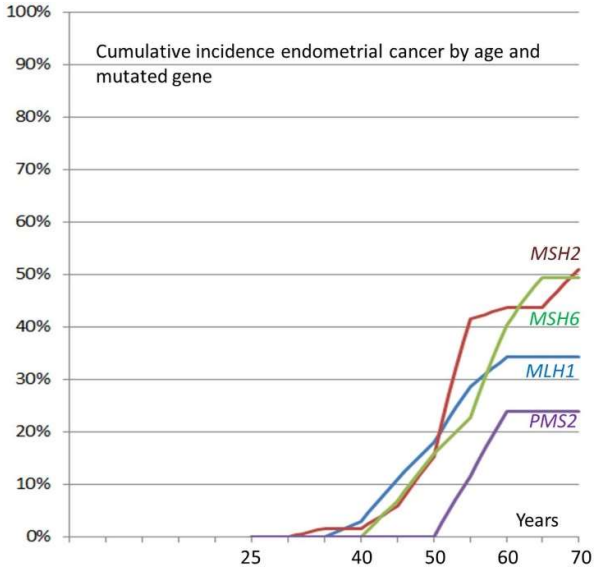

Figure 1 Calculated cumulative incidences by age and mutated gene for endometrial cancer as the first cancer by gene (Møller et al., 2017)

DEFINITION OF PROGNOSTIC RISK GROUPS INTEGRATING MOLECULAR MARKERS

- Histopathologic type, grade, myometrial invasion, and lymphovascular space invasion (LVSI) (no/focal/substantial) should be recorded in all patients with endometrial carcinoma. (EEE; V, A)
- The definition of prognostic risk groups is presented in Table 1 for both situations when molecular classification is known or unknown (Concin et al., 2020).

Table 1 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► 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, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► 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	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► 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	► 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	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial 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	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

*For stage III–IVA *POLE*mut endometrial 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 (eg, patients with both *POLE*mut and p53abn should be managed as *POLE*mut). ‡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. LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLE*mut, polymerase-mutated.

- Focal LVSI is defined as no more than five vessels with invasion. Extensive LVI (> five vessels) correlates with a negative prognosis (Bosse et al., 2015). (Belgian guidelines; IV, A)
- Different groups have applied a diagnostic algorithm using three immunohistochemical markers (p53, mutS homolog 6 (MSH6) and PMS1 homolog 2 (PMS2) and one molecular test (mutation analysis of the exonuclease domain of DNA polymerase epsilon (POLE) to identify prognostic groups analogous to the TCGA molecular-based classification (Figure 2) (Vermij et al., 2020).

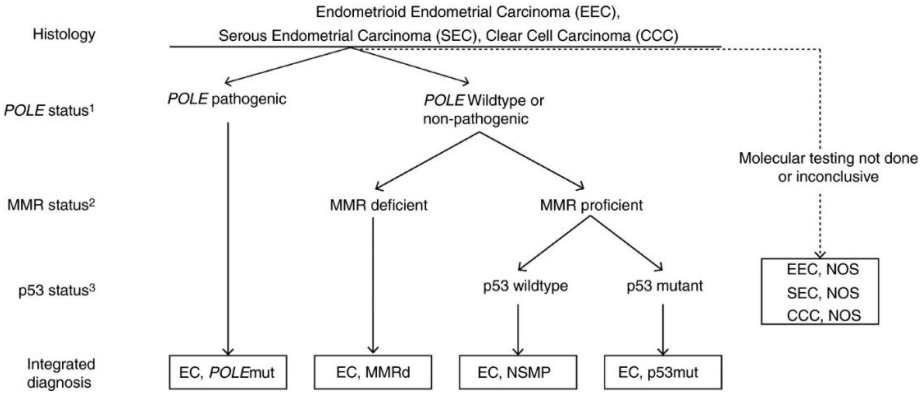

Figure 2 Diagnostic algorithm for a 'histomolecular' endometrial cancer classification. Pathogenic polymerase-epsilon (POLE) variants include: P286R, V411L, S297F, A456P and S459F. 2Mismatch repair protein (MMR) deficiency is defined by the loss of one or more MMR-proteins (MLH1, PMS2, MSH2 and MSH6). p53 immunohistochemistry (IHC) is an acceptable surrogate marker for *TP53* mutational status in MMR-proficient, *POLE* wild-type endometrial cancer (Vermij et al., 2020).

- Pathogenic POLE variants include: P286R, V411L, S297F, A456P and S459F. Mismatch repair protein (MMR) deficiency is defined by the loss of one or more MMR-proteins (MLH1, PMS2, MSH2 and MSH6). P53 immunohistochemistry (IHC) is an acceptable surrogate marker for TP53 mutational status in MMR-proficient, POLE wild-type endometrial cancer (Vermij et al., 2020).
- The Belgian Working Group for Gynecological Pathology made a large effort to convince reimbursement for POLE-mutation and p53 mutation, but it was rejected. The Working Group recommends testing in all endometrial cancers. Microsatellite instability (MSI) proteins are performed on any endometrial cancer, which gives an idea if there is MMR or not. For p53, it is more complicated as it might be heterogeneous and p53 IHC does not fit perfectly to p53 mutations. For POLE, there is no immunohistochemical substitute that can be used. The best way to define molecular subgroups is next-generation sequencing (NGS), although it is not yet reimbursed in Belgium.

SCREENING

- There is no evidence for routine screening in the general population. (Belgian guidelines; V, C)
- Patients receiving tamoxifen have a slightly increased incidence of endometrial cancer but routine screening is not recommended unless there is postmenopausal vaginal bleeding. (Belgian guidelines; IV, D)

- 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. (EEE; III, B)
- MMR IHC should not be performed on resection specimens following neoadjuvant chemo or radiotherapy, as this may induce a false negative signal. (Consensus WG; IV, C)

DIAGNOSIS

- Molecular classification is encouraged in all endometrial carcinomas. (EEE + adaptation WG; IV, B)
- Molecular testing should be done according the Belgian Compermed guidelines (https://www.compermed.be/nl/workflows/endometrium). (Consensus WG)
- The report should include invasion of cervical stroma (other stage) and uterine serosa. (Consensus WG; IV B)

STAGING

- For the classification of invasive endometrial cancer the FIGO-2018 classification is recommended (Belgian guidelines; IV, A) (Appendix 2).
- 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. (EEE; IV, 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. (EEE; IV, B)

Lymph node staging

- Sentinel lymph node (SLN) 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. (EEE; II, A)
- Processing of sentinel nodes in gynecological specimens has been addressed by the WG for Gynecological Pathology BSP. (Colpaert et al., 2019). The sentinel node should be cut in 2 mm sections and 3 levels (400 µm apart) and one IHC should be made. It is recommended that patients, for whom ultrastaging methods are applied differently from those recommended by the WG for Gynecological Pathology, should be included into clinical trials.
- Surgical LN staging should be performed in patients with high–intermediate-risk/high-risk disease. SLN biopsy is preferred above complete lymphadenectomy, unless there are pathological nodes on imaging. (EEE + adaptation WG; III, B)
- If SLN biopsy is performed (EEE; II,A)
    - Indocyanine green with cervical injection is the preferred detection technique.
    - Tracer re-injection is an option if SLN is not visualized upfront.
    - Side-specific systematic lymphadenectomy should be performed in high–intermediate-risk/ high-risk patients if SLN is not

detected on either pelvic side.

  - Pathologic ultrastaging of SLN is recommended.

- When performing a systematic lymphadenectomy, a complete pelvic lymphadenectomy is suggested or a para-aortic infrarenal LN dissection up to renal veins is indicated in the following conditions:
  - Grade 3 + deep myometrial invasion
  - Serosal invasion
  - Macroscopic adnexal metastases
  - Invaded pelvic LN
- Systemic pelvic lymphadenectomy should include at least 12 nodes (at least six on each side). When discussing cases where systemic lymphadenectomy is advisable/recommended then it is needed to define a certain number of nodes to be removed in order to avoid overtreatment with radiation therapy postoperatively. Chan et al. showed that removing 25 nodes will be associated with 85% chance of detecting node metastases, while removing 50 nodes will be associated with 100% detection rate (Chan et al., 2007). Brandon et al. showed that an increased LN count is associated with a 1% to 14% decreased hazard of death per each additional five LN removed and a 5% to 20% increased 5-year survival among women with pathologically node-negative endometrioid and serous endometrial. The recommended number in the study was 20 nodes (Seagle et al., 2017).
- Presence of both macrometastases and micrometastases (<2 mm, pN1(mi)) is regarded as a metastatic involvement. (EEE; IV, C)
- The prognostic significance of isolated tumor cells (ITC), pN0(i+), is still uncertain. The Cancer Staging Manual of the American Joint Committee on Cancer defines ITC as tumor cell clusters that are ≤0.2 mm at the largest diameter. (EEE; IV, C)
- If pelvic LN involvement is found intra-operatively, further systematic pelvic LN dissection should be omitted. However, debulking of enlarged LN and para-aortic staging can be considered. (EEE; IV, B)

PRE- AND INTRA-OPERATIVE WORK-UP

- Pre-operative mandatory work-up includes: personal and family history; general assessment and inventory of co-morbidities; menopausal status and medication, use of hormonal replacement therapy, child wish (in patients with childbearing potential), co-morbidities, geriatric assessment, if appropriate; full clinical examination, including pelvic examination; endometrial biopsy is mandatory. Pelvic magnetic resonance imaging (MRI) should be considered in high-risk disease unless there are radiologists/gynecologists who have specific expertise (as defined in the ESGO guidelines) in transvaginal or transrectal ultrasound. Disclaimer: MRI and US is only for the invasion-depth or for the invasion of the myometrium or cervical stroma. (EEE + adaptation WG; IV, C).
- Hysteroscopy is not recommended in patients with clear suspicion of endometrial cancer on gynecological ultrasound due to the increased incidence of the presence of malignant cells intraperitoneally after this procedure. (Belgian guidelines; IV, B)
- All patients should have at least abdominal/pelvic imaging by computed tomography (CT), [^{18}F]FDG positron emission tomography (PET)-CT, or MRI to assess ovarian, nodal, peritoneal, and other sites of metastatic

disease. (EEE + adaptation WG; IV, C)

- All patients, except for patients with low grade stage I disease, should have chest CT, [^{18}F]FDG PET-CT or whole-body MRI. (Consensus WG; IV, B).
- Cancer Antigen 125 (CA125) measurement can be useful in patients with high-risk disease (radiological IB, grade 3 and serous subtype) during treatment and for further follow-up. (Consensus WG; IV, C)
- Histopathologic tumor type and grade in endometrial biopsy are required. (EEE; IV, A)
- If there is no resection specimen, then MMR staining should be done on the biopsy. (Consensus WG; IV, A)
- Histologic confirmation should come before staging to allow for risk group allocation. (Consensus WG; IV, B)
- Histologic confirmation should also include molecular classification if possible. Required ancillary techniques are immunohistochemical analysis for p53 (at least), MSH-6 and PMS-2, complemented with MSH-2 and/or MLH-1, MLH-1 promotor hypermethylation in cases of MLH-1/PMS-2 decreased expression. (Consensus WG; IV, A)
- Intra-operative frozen section is not encouraged for myometrial invasion assessment because of poor reproducibility and interference with adequate pathologic processing. Take consideration to risk of false negative results. (EEE; IV, A)
- It is strongly discouraged to perform gross examination of the uterus outside the pathology lab. (Consensus WG; IV, D)

EARLY STAGE DISEASE

SURGICAL MANAGEMENT OF APPARENT STAGE I/II ENDOMETRIAL CARCINOMAS

Minimally invasive approach

- Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma. (EEE; I, A)
- Any intra-peritoneal tumor spillage, including tumor rupture or morcellation (including in a bag), should be avoided. (EEE; III, B)
- If vaginal extraction risks uterine rupture, other measures should be taken (eg, mini-laparotomy, use of endobag). (EEE; III, B)
- Tumors with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications for minimally invasive surgery. (EEE; III, B)

Standard surgical procedures

- Standard surgery is total hysterectomy with BSO without vaginal cuff resection. (EEE; II, A)
- 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. (EEE; IV, 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. (EEE; IV, B)

Lymph node staging

- SLN 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. (EEE; II, A)
- Surgical LN staging should be performed in patients with high–intermediate-risk/high-risk disease. SLN biopsy is an acceptable alternative to systematic lymphadenectomy for LN staging in stage I/II. (EEE; III, B)
- If SLN biopsy is performed (EEE; II, A):
    - Indocyanine green with cervical injection is the preferred detection technique.
    - Tracer re-injection is an option if SLN is not visualized upfront.
    - Side-specific systematic lymphadenectomy should be performed in high–intermediate-risk/high-risk patients if SLN is not detected on either pelvic side.
    - Pathologic ultrastaging of SNL is recommended.
- When a systematic lymphadenectomy is performed, pelvic and para-aortic infrarenal lymph node dissection is suggested. (EEE; III, B)
- Presence of both macrometastases and micrometastases (<2 mm, pN1(mi)) is regarded as a metastatic involvement. (EEE; IV, C)
- The prognostic significance of ITCs, pN0(i+), is still uncertain. (EEE; IV, C)
- If pelvic LN involvement is found intra-operatively, further systematic pelvic LN dissection should be omitted. However, debulking of enlarged LN and para-aortic staging can be considered. (EEE; IV, B)

Option for ovarian preservation and salpingectomy in stage I/II

- 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. (EEE; IV, A)
- In cases of ovarian preservation, salpingectomy is recommended. (EEE; IV, B)
- Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (eg, BRCA mutation, Lynch syndrome, etc). (EEE; IV, B)

Radicality of surgery for clinical stage II

- Total hysterectomy with BSO and LN staging is the surgical standard of care in patients with stage II endometrial carcinoma. (EEE; IV, B)
- More extensive procedures should only be performed if required to achieve free surgical margins. (EEE; IV, B)

Medically unfit patients

- Medical contra-indications to the standard surgical management by minimally invasive surgery are rare. Vaginal hysterectomy, with BSO if

feasible, can be considered in patients unfit for the recommended standard surgical therapy. (EEE; IV, C)

- Definitive radiotherapy can be considered for primary tumors where surgery is contra-indicated for medical reasons:
    - The combination of External beam radiotherapy (EBRT) and brachytherapy should be used for high-grade tumors and/or deep myometrial invasion. (EEE; II, B)
    - For low-grade tumors, brachytherapy alone can be considered (EEE; II, B)
    - In medically unfit patients unsuitable for curative surgery or radiotherapy, systemic treatment (including hormonal therapy) can be considered. (EEE; IV, B)

Fertility preservation

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 atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN) or grade 1 endometrioid endometrial carcinoma without myometrial invasion and without genetic risk factors. (EEE; V, A)
- In these patients, endometrial biopsy, preferably through hysteroscopy, must be performed. (EEE; III, A)
- AH/EIN or grade 1 endometrioid endometrial carcinoma must be confirmed/diagnosed by a pathologist experienced in gynecological pathology. (EEE; V, A)
- Radiologic imaging to assess the extension of the disease must be performed. An expert ultrasound examination can substitute pelvic MRI scan. (EEE; III, B)
- 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. (EEE; V, A)
- 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. (EEE; IV, B)

Management and follow-up for fertility preservation

- Hysteroscopic resection prior to progestin therapy can be considered. (EEE; III, 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. (EEE; IV, 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. (EEE; IV, B)

- Continuous hormonal treatment should be considered in responders who wish to delay pregnancy. (EEE; IV, 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. (EEE; IV,B)
- Fertility-sparing treatment can be considered for intrauterine recurrences only in highly selected cases under strict surveillance. (EEE; IV, C)
- 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. (EEE; IV, B)

ADJUVANT TREATMENT

Treatment low-risk group

- For patients with low-risk endometrial carcinoma, no adjuvant treatment is recommended. (EEE; I, 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. (EEE; III, A)

Treatment intermediate risk group

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

Treatment high-intermediate risk group (pN0 after lymph node staging)

- Adjuvant brachytherapy can be recommended to decrease vaginal recurrence in case of LVSI negative or stage I/II grade 1. (EEE + adaptation WG; II, B)
- EBRT can be considered for substantial LVSI and for stage II. (EEE; I, B)
- Adjuvant chemotherapy can be considered, especially for high-grade (grade III) and/or substantial LVSI. (EEE; II, C)
- Omission of any adjuvant chemotherapy is an option. (EEE; IV, C)
- When molecular classification is known, POLEmut and p53abn have specific recommendations (see respective recommendations for low- and

high-risk).

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

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

High risk

- EBRT with concurrent and adjuvant chemotherapy (EEE; I, A) or alternatively sequential chemotherapy and radiotherapy is recommended. (EEE; I, B)
- Chemotherapy alone is an alternative option. (EEE; I, B)
- Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas). (EEE; IV, B)
- Intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) should be done in case of EBRT. (EEE + adaptation WG; I, A)
- In case of positive common iliac/PAO LN, paraortic LN irradiation should be considered. (EEE + adaptation WG; I, A)
- Additional brachytherapy can be considered in case of cervical stromal invasion (stage II-IV).
- When the molecular classification is known, p53abn carcinomas without myometrial invasion and POLEmut have specific recommendations (see respective recommendations for low- and intermediate-risk). (EEE; III, C)

ADVANCED DISEASE

Surgically treated stage III and IV disease

- In stage III and IV endometrial carcinoma (including carcinosarcoma), surgical tumor debulking including enlarged LN 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. (EEE; IV, B)
- Primary systemic therapy should be used if upfront surgery is not feasible or acceptable. (EEE; IV, A)
- In case of a good response to systemic therapy, delayed surgery can be considered. (EEE; IV, C)
- Only enlarged LN or FDG positive LN should be resected. Systematic lymphadenectomy is not recommended. (EEE + adaptation WG; IV, B)
- Adjuvant radiotherapy should be considered in stage III-IVA (Consensus WG; I, A) and in some cases of stage IVB. (Consensus WG; IV, A)

Unresectable primary tumor due to local extent of disease

- For unresectable tumors, multi-disciplinary team discussion should consider definitive radiotherapy with EBRT and intra-uterine brachytherapy, or neoadjuvant chemotherapy prior to surgical resection or definitive radiotherapy, depending on response. (EEE; IV, C)
- Image-guided brachytherapy is recommended to boost intrauterine, parametrial, or vaginal disease. (EEE; IV, A)
- Chemotherapy should be considered after definitive radiotherapy. (EEE; IV, B)

Residual pelvic or para-aortic lymph nodes following surgery

- Residual LN disease should be treated with a combination of chemotherapy and EBRT (EEE; III, B) or chemotherapy alone. (EEE; IV, B)
- EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost. (EEE; IV, B)

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

- An individualized approach with either radiotherapy or chemotherapy or a combination of both modalities should be considered by a multi-disciplinary team. (EEE; V, B)

RECURRENT DISEASE

Radiotherapy naïve patients

- Patients with recurrent disease (including peritoneal and LN 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. (EEE; IV, C)
- In selected cases, palliative surgery can be performed to alleviate symptoms (eg, bleeding, fistula, bowel obstruction). (EEE; IV, B)
- For locoregional recurrence, the preferred primary therapy should be EBRT ± chemotherapy with brachytherapy. (EEE; IV, A)
- An easily accessible superficial vaginal tumor can be resected vaginally prior to radiotherapy. (EEE; IV, C)
- For vaginal cuff recurrence:
    - Pelvic EBRT + intracavitary (±interstitial) image-guided brachytherapy is recommended. (EEE; IV, A)
    - In case of superficial tumors, intracavitary brachytherapy alone can be considered. (EEE; IV, A)
- Systemic treatment can be considered before or after radiotherapy (EEE; IV, C)

Radiotherapy pre-treated patients with locoregional recurrence

- In patients with a history of previous radiation, radical surgery, including exenteration, should be considered when the intention is complete resection with clear margins (EEE; IV, B). Vaginectomy can be sufficient in certain cases with limited disease and the possibility to achieve negative section margins (Consensus WG; IV, C)
- Additional options to consider include intra-operative radiation therapy or other forms of radiation therapy. (EEE; IV, 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). (EEE; IV, C)
- In patients who only had previous brachytherapy, EBRT + brachytherapy boost is recommended. (EEE; IV, C)
- In patients where re-irradiation with ERBT is not an option, image-guided interstitial brachytherapy only is recommended (may improve outcome) (EEE; IV, C)

Oligometastatic recurrent disease

- [^{18}F]FDG PET-CT or diffusion-weighed MRI is recommended for patients to rule out other metastatic disease. (Consensus WG; IV; A)
- Patients with oligometastatic disease should be considered for radical local therapy (EEE; IV, B)
- Treatment options include (EEE; IV, B):
    - Surgery
    - Radiation therapy including stereotactic radiotherapy
    - Local ablating techniques
- The additional benefit of systemic treatment after radical local therapy is uncertain. (EEE; IV, B)
- Complete resection of distant oligometastases and recurrence of the pelvic or retroperitoneal LN may be considered if technically possible based on the localization of the disease and expected morbidity. (Consensus WG; IV B)
- The histological type (endometrioid versus non endometrioid) should not influence the decision whether or not to proceed with surgery
- After complete resection, adjuvant radiotherapy could be considered in selected cases. (Consensus WG; V, C)

Systemic treatment for recurrent disease and palliative radiotherapy

- Hormone therapy is the preferred front-line systemic therapy for patients with low-grade carcinomas without rapidly progressive disease (ER and PR positive, long disease-free survival (DFS)). (EEE + adaptation WG; II, A)
- Chemotherapy is the preferred therapy for patients with high-grade carcinomas (grade 3) and patients who have short DFS. (Consensus WG)
- Progestogens (medroxyprogesterone acetate 200 (–300) mg and megestrol acetate 160mg) are recommended. (EEE; III, A)

- Alternative options for hormonal therapies include aromatase inhibitors, tamoxifen and fulvestrant. (EEE; III, C)
- The standard chemotherapy treatment is carboplatin AUC 5–6 + paclitaxel 175mg/m^2 every 21 days for six cycles. (EEE; I, A)
- There is no standard of care for second-line chemotherapy. (EEE; IV, C)
- In patients with a long platinum-free interval, re-introduction of platinum can be considered. (EEE; IV, C)
- Anti-PD1-based immune therapy is a treatment option in dMMR/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen (Garnet trial and Keynote 158 trail; Marabelle et al., 2020; Oaknin et al., 2020). Dostarlimab will be available in the next months in Belgium (EMA approved In April 2021)(Consensus WG; II A)
- Lenvatinib/pembrolizumab is a treatment option regardless of MMR status, in patients with endometrial cancer progressing after prior platinum-based therapy (Marabelle et al., 2020). This treatment only received FDA approval. It is not yet approved by EMA and not yet reimbursed in Belgium. (Consensus WG; I,A)
- Letrozole is a proven hormonal therapy, but is not yet reimbursed (ENGOT-EN3/NSGO-PALEO trial; Mirza et al., 2020). (Consensus WG, II A)
- Radiotherapy is indicated for palliation of symptoms related to pelvic or systemic disease. (EEE; IV, A)
- Hypofractionated small volume EBRT can be used for treating primary disease in patients not fit for radical treatment. (EEE; IV, B)

FOLLOW-UP

- Follow-up consultations could be provided every 3 months in the first two years, every 6 months until 5 years after diagnosis, and every year after 5 years. The TOTEM trial will be published in the near future. (Belgian guidelines + TOTEM trial; V, C)
- Clinical and vaginal examination is recommended at every follow-up consultation in all cases who can be treated with curative intent at the time of recurrence, e.g. patients who did not receive postoperative radiotherapy or who might be candidates for exenterative surgery. (Belgian guidelines; IV, B)
- There is no evidence that routine imaging to screen for distant recurrent disease in asymptomatic patients with normal clinical findings has a survival benefit. (Consensus WG; IV, B)
- There is no evidence that CA125 measurement and cytological vaginal follow-up has a survival benefit in asymptomatic patients with normal clinical findings. (Consensus WG; V, C)

Appendix I: FIGO Staging 2018 (surgical staging)

Stage I: Tumor confined to the corpus uteri
Stage IA G 123: no invasion or < ½ of the myometrium
Stage IB G 123: invasion of ≥ ½ of the myometrium

Stage II: Tumor invades cervical stroma (but does not extend beyond the uterus).

Stage III: Local and/or regional spread of the tumor
Stage IIIA G 123: invasion of the serosa of corpus uteri and/or adnexae (positive peritoneal cytology has to be reported separately and is in itself not sufficient to be classified as stage III)
Stage IIIB G 123: invasion of the vagina or parametrial involvement
Stage IIIC G 123: pelvic and/or para-aortic lymph nodes metastasis
- IIIC1: Pelvic lymph nodes metastasis
- IIIC2: Para-aortic lymph nodes metastasis

Stage IV: Tumor invades bladder mucosa and/or bowel mucosa, and/or distant metastasis
Stage IVA G 123: invasion of bladder mucosa and/or bowel mucosa
Stage IVB G 123: distant metastasis with involvement of intra-abdominal and/or inguinal lymph nodes

G1, 2 of 3 is the histopathological grading

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