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CLINICAL GUIDES IN ONCOLOGY

SEOM-GEICO clinical guidelines on endometrial cancer (2025)

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Abstract

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries. Although most cases are diagnosed at an early stage, prognosis in case of relapse or metastasis remains poor. Molecular characterization of EC is highly recommended as it allows more accurate risk stratification and may modify treatment recommendations. The updated FIGO 2023 staging of EC highlights the importance of traditional clinicopathological factors, while underlining the need for molecular classification to predict outcomes. In early-stage EC, standard treatment consists of total hysterectomy and bilateral salpingo-oophorectomy. Lymph node evaluation remains controversial, as the benefits of systematic lymphadenectomy are unclear. Adjuvant treatment, consisting of radiotherapy, brachytherapy, and chemotherapy, should be chosen according to risk category. In women with advanced or recurrent EC, the combination of carboplatin and paclitaxel has long been standard treatment. However, therapeutic options have changed recently due to advances in immunotherapy. The aim of this guideline is to summarize the current evidence for the diagnosis, treatment, and follow-up of EC, and to provide evidence-based recommendations for clinical practice.

Keywords Endometrial cancer · Guideline · Diagnosis · Treatment · Follow-up

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Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in Spain, surpassing ovarian and cervical cancer. According to the latest data from the Spanish Ministry of Health, 6,600 new cases were diagnosed in 2024 [1]. Its incidence has steadily increased in recent decades, largely driven by rising rates of obesity, type 2 diabetes, and an aging population [2]. Although most cases are diagnosed at an early stage, advanced or recurrent disease continues to be linked to poor outcomes. The 2023 FIGO classification integrates molecular features with traditional clinicopathological parameters, enabling more accurate risk stratification and guiding treatment decisions [3]. This shift reflects the impact of genomic studies, such as The Cancer Genome Atlas (TCGA), which have redefined the biological understanding of EC. In early-stage disease, standard treatment remains surgical, while the role of lymphadenectomy and adjuvant therapy should be individualized. In advanced stages, immunotherapy has transformed the EC treatment landscape. This guideline reviews the current evidence and provides practical recommendations for the diagnosis, treatment, and follow-up of EC.

Methods

This guideline is based on a systematic review of relevant published studies and the consensus of ten expert oncologists from the Spanish Society of Medical Oncology (SEOM) and the Spanish Gynecological Cancer Research Group (GEICO). The Infectious Diseases Society of America US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines [4] has been used to assign levels of evidence and grades of recommendation. Recommendations on systemic treatment for EC have been made considering options currently financed by the Spanish public health system. SEOM-GEICO recommendations for diagnosis and treatment of locoregional and metastatic/recurrent endometrial cancer are summarized in Table 1.

Incidence and epidemiology

Endometrial cancer (EC) is the most common gynecological neoplasm in developed countries and the second most common gynecological cancer worldwide after cervical cancer. Its incidence has increased significantly in recent decades, largely due to the ageing of the population and an increase in predisposing factors such as obesity, diabetes, and hypertension [5]. Other factors such as nulliparity, the use of unopposed estrogen therapy, early menarche, and late menopause have also been associated with increased risk [6]. In localized stages, EC is associated with a 5-year overall survival of over 80%, although an increasing age-adjusted mortality rate has been observed in recent decades, especially among patients under 50 and Black women [7]. However, in patients who relapse or present with metastases upon diagnosis, the 5-year survival rate is around 20% [8].

Diagnosis, pathology and molecular biology

1. **Diagnosis**

A diagnostic workup focusing on possible EC must be carried out in patients presenting with abnormal uterine bleeding, regardless of quantity, especially in postmenopausal women or those with risk factors for EC.

Transvaginal ultrasound is a simple, inexpensive, and widely available tool, and as such is the first recommended test for diagnostic workup. Despite the lack of clear consensus on the cut-off value for normal endometrial thickness (ET) in postmenopausal women, a cut-off level of 3 mm is highly sensitive (97%) for ruling out EC. In asymptomatic women with incidental findings, a higher threshold of up to 8 mm may be acceptable, and invasive testing may be withheld in cases of ET between 3 and 8 mm [9] [II, B].

Endometrial biopsy should be performed using aspiration devices, despite a false positive rate of 10%. In cases of persistent abnormal bleeding, dilatation and curettage is preferred over hysteroscopy, as curettage usually provides a more comprehensive assessment of the endometrium and a more accurate characterization of histological findings. However, in the case of focal lesions such as polyps, these techniques may be considered complementary [10] [II, B].

Preoperative imaging techniques should be performed depending on histological and ultrasound findings. In apparently localized, low-grade tumors, pelvic magnetic resonance imaging (MRI) is recommended because of its superiority in assessing myometrial invasion, pathological lymph nodes, and cervical involvement. In high-grade tumors or if extrauterine involvement is suspected, an abdominal and thoracic computed tomography (CT) scan should also be ordered. Positron emission tomography (PET-CT) may also be helpful in this scenario, although it is not universally available, and its superiority has not been demonstrated [11] [IV, B].

The role of tumor markers in the diagnostic process is controversial. Elevated levels of Ca125 and HE4 have been reported in patients with nodal involvement at diagnosis [12, 13].

Table 1 SEOM-GEICO recommendations for the diagnosis and treatment of locoregional and metastatic/recurrent endometrial cancer

Diagnosis and staging	LE, GoR
Endometrial sampling via biopsy or dilatation and curettage is an acceptable initial method for diagnosing EC	IV, A
Preoperative assessment for EC must include clinical examination, transvaginal ultrasound, and pelvic MRI	IV, B
For assessment of extrapelvic disease, additional imaging tests, including thoracic and abdominal CT scans or FDG-PET-CT, may be considered	IV, C
Hereditary syndromes should be evaluated, and genetic counselling should be offered to patients with positive test results	III, A
Performing molecular classification is recommended in patients diagnosed with EC for more accurate risk stratification and more precise choice of treatment	III, A
The FIGO 2023 update for EC staging incorporates molecular factors and emphasizes risk classification. The changes aim to provide a stronger evidence-based framework for treatment recommendations and a more precise approach to recovery outcomes and survival data in the future	III, A
Treatment of locoregional disease	
Standard surgery for early-stage EC includes total hysterectomy and bilateral salpingo-oophorectomy	I, A
Fertility-sparing treatment may be considered for reproductive-age women with stage IA (FIGO 2023) endometrioid endometrial carcinoma, without risk factors for recurrence, and who express a desire for future childbearing	IV, A
Sentinel lymph node biopsy can be considered for staging purposes in patients with low- or intermediate-risk disease	II, A
In patients with high-intermediate and high-risk stage I-II EC, sentinel lymph node biopsy may serve as an alternative to lymphadenectomy	III, B
In SC, UCS, or undifferentiated carcinomas, an inframesocolic omentectomy should also be performed	IV, B
For low-risk EC, no adjuvant therapy is recommended	II, A
For intermediate risk EC, adjuvant vaginal BT is recommended	I, A
For intermediate risk EC, no adjuvant therapy may be considered for some patients	III, C
For high-intermediate risk EC, adjuvant EBRT is recommended	II, A
For high-intermediate risk EC, BT may be considered for patients with pN0 lymph node staging	II, B
For high-risk EC, EBRT with concurrent ChT may be considered	I, A
For high-risk EC, ChT and sequential RT may be considered	I, B
For high-risk EC, ChT followed by BT can be considered	I, B
Treatment of metastatic and recurrent disease	
For isolated pelvic recurrence or single metastatic sites, surgical resection, radiotherapy, or ablative therapy may be considered, followed by systemic therapy although its benefit is uncertain	IV, B
Enrolment in clinical trials is strongly recommended	V, B
Chemo-immunotherapy followed by maintenance immunotherapy (2 years with pembrolizumab or 3 years with dostarlimab) is the standard first line treatment for dMMR and pMMR populations. The level of evidence is different for dMMR I, A and pMMR I, B	I, B
The addition of a PARPi to chemo-immunotherapy could be another option in the pMMR population. This treatment option will not be reimbursed by the Spanish public health system	I, B
In patients with pMMR relapsed disease after prior chemotherapy in the adjuvant/neoadjuvant setting, the combination of pembrolizumab and lenvatinib may be considered if chemotherapy is contraindicated	III, C
Potential second line treatments for dMMR immunotherapy-naive patients after platinum-based first line therapy include dostarlimab or pembrolizumab	III, A
The combination of pembrolizumab and lenvatinib is a potential second line treatment for dMMR immunotherapy-naive patients after platinum-based first line therapy	I, B
In immunotherapy-naïve pMMR patients, the pembrolizumab-lenvatinib combination is recommended as second-line therapy	I, A
After immunotherapy, a rechallenge with platinum-based chemotherapy or monochemotherapy should be considered as second line treatments	II, B
For HER2 positive patients, anti-HER2 therapy should be considered	II, B
Hormonal therapy could be an appropriate therapeutic alternative for patients with low-grade, hormone-receptor positive EC, without rapidly progressive and/or high-volume metastatic disease	II, A
Follow-up after initial treatment	
In low-risk patients, surveillance with physical and gynecological examinations is recommended every 6 months for the first 2 years, and then annually until completing 5 years of recurrence-free follow-up	V, C
For high-risk groups, surveillance with physical and gynecological examinations are recommended every 3 months for the first 2 years, and then every 6 months until completing 5 years of recurrence-free follow-up	V, C
A CT scan or PET-CT may be considered for the evaluation of a suspected recurrence	V, C
All EC survivors should be counselled regarding the importance of avoiding obesity and ensuring regular exercise and a healthy diet	II, B

BT, brachytherapy; ChT, chemotherapy; dMMR, mismatch-repair deficient; EC, endometrial cancer; ERBT, external beam radiotherapy; GoR, grade of recommendation; LE, level of evidence; pMMR, MMR proficient; RT, radiotherapy; SC, serous carcinoma; UCS, uterine carcinosarcoma

2. Hereditary endometrial cancer and screening

Approximately 5% of ECs are associated with Lynch syndrome, an autosomal dominant cancer susceptibility syndrome caused by germline mutations in DNA mismatch repair (MMR) genes (MSH2, MLH1, MSH6 and PMS2) or by an EPCAM deletion (EPCAM -MSH2) [14] [IV, A].

Lynch syndrome screening is currently recommended for all cases of EC regardless of age or histological type [15] [II, A]. The first step of the diagnostic algorithm is to perform immunohistochemistry (IHC) on tumor tissue to demonstrate loss of MMR protein function (MMR deficiency or dMMR). If MLH1 protein loss is identified, MLH1 promoter should be tested for methylation or a less common *BRAF* mutation to rule out a non-hereditary cause. If none of these are identified, the final step is to carry out germline analysis of MMR genes to determine whether the patient has a Lynch syndrome-associated mutation or if the MMR deficiency can be attributed to double somatic mutations (Lynch-Like Syndrome).

Genetic counselling should be offered to all Lynch syndrome carriers, for whom the estimated lifetime risk of developing EC ranges between 21%–51%. Carriers of MSH2 (51%) and MSH6 (49%) mutations are at highest risk, and carriers of MLH1 (34%) and PMS2 (12–24%) mutations at lower risk [16] [III, B].

Other, less frequent hereditary ECs can be caused by:

- *PTEN* germline mutations in Cowden syndrome (< 1% of ECs), with up to a 25% increase in risk [17].
- Germline mutations in *BRCA1/2* (1% of EC), with an overall lifetime risk of 3%, and 1.1% for serous type EC [18].
- *STK11* gene mutations in Peutz-Jeghers syndrome that increase lifetime risk by 9%[19].

3. Pathology and molecular classification

The histological classification of EC is based on the World Health Organization (WHO) guidelines and focuses on tumor histopathology [20]. Endometroid carcinomas (grade 1 to 3) (EEC) are the most frequent type of EC, accounting for 80–90% of all ECs. Serous carcinomas (SC) represent 3–10% of all cases and are associated with poor outcomes. Other, rarer subtypes include clear cell carcinoma, carcinosarcoma (UCS), mucinous, neuroendocrine, undifferentiated and dedifferentiated, mesonephric, mesonephric-like, and squamous cell EC [21].

Historically, The Cancer Genome Atlas (TCGA) classified ECs into four categories, including POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high subgroups [22]. Each subgroup featured different molecular characteristics and prognosis. Subsequently, Talhoulk and colleagues proposed a molecular classification based on surrogate markers that are more available in clinical practice [23]. These surrogate markers include: 1) sequencing of the exonuclease domain of the DNA polymerase epsilon (POLE), in which those with pathogenic variants are classified as POLE mutant (POLEm) subgroup; 2) MMR proteins (MLH1, PMS2, MSH2, MSH6) IHC, defining those with loss of one or more proteins as MMR deficient (dMMR); 3) p53 IHQ, defining p53 abnormal (p53abn) subgroups; and 4) none of the previous, classified as non-specific molecular profile (NSMP). Table 2 describes the main characteristics of each molecular subgroup [24].

The dMMR subgroup is primarily assessed using IHC to detect loss of MMR proteins. Microsatellite instability (MSI) assays, which are typically polymerase chain reaction (PCR)-based, are highly concordant with IHC. The microsatellite instability-high (MSI-h) designation applies to tumors demonstrating instability in microsatellite regions due to MMR deficiency. IHC is often preferred due to its ability to identify the specific defective protein, its lower cost, and widespread availability. Several studies have demonstrated the high prognostic impact of the molecular classification, independently of histological subtype and grade, with POLEm tumors associated with excellent prognosis, dMMR and NSMP tumors intermediate, and p53abn ECs poor prognosis [24]. Molecular subgroups have also proven relevant when tailoring adjuvant therapy, and as potential biomarkers of response to systemic therapy and immune checkpoint inhibition.

"Multiple classifiers" are defined as ECs that exhibit molecular features of more than one classification group (for example, p53abn and dMMR), with prognosis and treatment guided by the most favorable classifier [24].

Cost and access are major barriers to universal testing, particularly *POLE* analysis. In resource-limited settings or in situations in which further testing will not modify recommendations for treatment, such as certain stage IA grade 1/2 EECs (p53 wild type (p53wt), MMR proficient (pMMR), lymphovascular invasion (LVSI) negative), omitting *POLE* analysis may be considered [25].

The evaluation of estrogen receptor (ER) status by IHC is also recommended at diagnosis, due to its prognostic value in NSMP and its predictive value for treatment response in advanced disease [IV, A]. Although there is no consensus regarding the cut-off for ER positivity, the currently defined threshold of 10% is based on the analysis of the most recent studies, as it provides the best prognostic discrimination between ER-positive and ER-negative NSMP tumors. These groups were incorporated into the

Table 2 Main characteristics of each molecular subtype

	POLEm	dMMR	NSMP	p53abn
Frequency	5–15%	20–30%	30–60%	10–25%
Surrogate marker	POLE sequencing Other: Hotspot target sequencing	MMR protein IHC Other: MSI assay		p53 IHC Other: TP53 sequencing
Molecular characteristics	Ultramutated–High TMB (>100 mut/Mb) Somatic CNA low 20% dMMR/MSI 20% p53mut	Hypermutated–High TMB (>10 mut/Mb) Somatic CNA low MSI 10% p53mut	Low TMB Somatic CNA low pMMR/MSS p53wt	Low TMB Somatic CNA high pMMR/MSS p53mut 20-25% Her2 amplifications
Frequent histological characteristics	High grade endometrioid High immune infiltrate	High grade endometrioid LVSI+ High immune infiltrate	Low grade endometrioid ER/PR positivity	High grade of all histologies (++ serous) LVSI+
Frequent clinical characteristics	Early stage	High BMI	High BMI	Advanced stage Distant recurrences
Prognosis	Very good	Intermediate	Intermediate –Worse in ER negative –Histology and grade dependent	Poor

POLEm, POLE mutant; dMMR, MMR deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; IHC, immunohistochemistry; MSI, microsatellite instability; CAN, copy number alterations; TMB, tumor mutational burden; pMMR, MMR proficient; MSS, microsatellite stable; p53wt, p53 wild-type; LVSI, lympho-vascular invasion; ER, estrogen receptor; PR, progesterone receptor; BMI, body mass index

four-group molecular classification model, showing clear differences in prognosis, with significantly worse recurrence-free survival observed in the ER-negative NSMP group [26].

Staging and risk assessment

ECs are staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) system, and preoperative staging is crucial for risk classification and surgical planification. This approach primarily focuses on evaluating myometrial and cervical invasion, as well as lymph node metastasis.

In June 2023, the FIGO Women's Cancer Committee presented a new staging system for EC, replacing the 2009 version [27]. The revised cancer staging system (FIGO 2023) [3] introduces important updates (Table 3). Stages I and II now consider non-anatomical factors, including histological type, grade, LVSI, and molecular subgroups. Stages III and IV are refined by distinguishing tumor location (vaginal vs. parametrial) and metastasis size (micrometastasis vs. macrometastasis). Additionally, patients with uterine and ovarian involvement are categorized into stage IA3, indicating a favorable prognosis, and stage IIIA1, indicating a poorer prognosis. These changes enhance the precision of cancer staging and prognostic evaluation.

Treatment

Locoregional disease

1. **Surgical Management**

Surgery is crucial in the management of early-stage EC. The primary goal of surgery is complete removal of disease. In addition, surgical staging helps to determine risk of recurrence and need of adjuvant therapy. Standard surgery includes total hysterectomy and bilateral salpingo-oophorectomy [I, A]. Lymph node evaluation is also recommended for these patients. For patients with disease localized to the uterus, minimally invasive surgery techniques, such as laparoscopy or robotic surgery, are recommended. In SC, USC and undifferentiated carcinomas, inframesocolic omentectomy should be also performed [28, 29] [IV, B].

Fertility-sparing treatment should be considered for reproductive-age women with stage IA FIGO 2023 EEC, without risk factors for recurrence, and who desire future childbearing [IV, A]. A combined approach, consisting of hysteroscopic tumor resection followed by oral progestins and/or a levonorgestrel intrauterine device, is the most effective fertility-sparing option, offering the highest rates of complete response and live births compared to other treatments [II, B]. However, this option is contraindicated in patients with *BRCA*1/2 germline mutations. In cases involving other hereditary syndromes, such as Lynch syndrome, the decision should be individualized [30].

Table 3 Endometrial cancer (FIGO 2023) staging system

Stage	Description
I	Confined to the uterus and ovary
IA	Disease limited to the endometrium or non-aggressive histology[a], with < 50% invasion of the myometrium and no or focal LVSI
IA1	Tumor with non-aggressive histology, limited to a polyp or confined to the endometrium (no myometrial invasion)
IA2	Tumor with non-aggressive histology and < 50% myometrial invasion without LVSI or focal invasion
IA3	Low grade endometrioid carcinomas limited to the uterus and ovary[b]
IB	Non-aggressive tumor histology and invasion > 50% of the myometrium without LVSI or focal invasion
IC	Aggressive tumor histology[a] limited to polyp or confined to the endometrium (no myometrial invasion)
II	Invasion of the cervical stroma without extrauterine involvement or substantial LVSI[c] or aggressive histologies with myometrial invasion
IIA	Non-aggressive histology, but cervical stroma involvement
IIB	Non-aggressive histology, but substantial LVSI
IIC	Aggressive histology tumor with any myometrial involvement
III	Tumor with regional involvement of any histology
IIIA1	Tumor with invasion of the ovary or fallopian tube (except when meeting stage IA3 criteria)
IIIA2	Involvement of the uterine subserosa or spread through uterine serosa
IIIB1	Tumor with dissemination in parametria and/or vagina
IIIB2	Dissemination in the pelvic peritoneum
IIIC1	Metastasis to pelvic lymph nodes
IIIC1i	Micrometastasis[d]
IIIC1ii	Macrometastasis[e]
IIIC2	Metastasis in para-aortic lymph nodes up to the renal vessels
IIIC2i	Micrometastasis[d]
IIIC2ii	Macrometastasis[e]
IV	Tumor affects the bladder or bowel mucosa, or distant dissemination
IVA	Tumor invades bladder or bowel mucosa
IVB	Peritoneal dissemination beyond the pelvis
IVC	Distant metastasis, including to lymph nodes above the renal vessels
Stage	Molecular findings in stage I-II EC
$IAm_{POLEmut}$	POLEmut EC, confined tu the uterus or with cervical extensión, regardless of the degree of LVSI or histological type
$IICm_{p53abn}$	P53abn EC, confined to the utreus with any myometrial invasion , with or without cervical invasion, and regardless of the degreeof LVSI or histological type

EEC, endometrioid carcinoma; ITCs, isolated tumor cells; LVSI, lympho-vascular space invasion; SC, serous carcinoma; UCS, uterine carcinosarcoma; WHO: World Health Organization

[a]Non-aggressive histological types are composed of low-grade (G1 and 2) EECs. Aggressive histological types are composed of high-grade EEC (G3), SC, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and UCS

[b]Extensive/substantial LVSI is defined by WHO 2021 as involving if ≥5 vessels

[c]Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a)

[d]Micrometastases are considered metastatic involvement (pN1 (mi)). The prognostic significance of isolated tumor cells (ITCs) is unclear. The presence of ITCs should be documented and is regarded as pN0(i+)

[e]According to TNM, macrometastases are > 2 mm in size, micrometastases are 0.2–2 mm and/or > 200 cells, and isolated tumor cells are ≤ 0.2 mm and ≤ 200 cells

When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis. Molecular subtype assignment can be done on a biopsy, in which case it need not to be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages

In FIGO stages I and II the stage category is modified by molecular classification in case of POLEmut or p53abn status. This is depicted in the stage by the addition of "m" for the molecular classification, and a subscript is added to denote POLEmut or p53abn status, as shown above

FIGO stages III and IV are not modified by molecular classification, however, the molecular classification should be recorded if known

The evaluation of lymph nodes in EC remains controversial, and the benefits of systematic lymphadenectomy (LND) are unclear. Sentinel lymph node (SLN) mapping has emerged as an alternative to LND. Pathological ultrastaging after routine hematoxylin and eosin staining has led to an increased detection rate of SLN metastases [31]. However, whether a positive pelvic SLN is indication of further retroperitoneal staging (pelvic and/or para-aortic LND) remains controversial. When pelvic SLN involvement is identified, para-aortic LN staging should be considered. Based on available data, SLN biopsy may be considered for staging purposes in patients with low or intermediate-risk disease and may serve as an alternative to LND in high-intermediate and high-risk stage I-II patients. Currently, the ECLAT (NCT03438474) and SEPAL-3 [32] clinical trials are exploring the impact of pelvic and para-aortic LND on overall survival (OS) in high-risk patients with FIGO stages I and II EC.

For patients with stages III and IV EC, cytoreductive surgery to attempt complete resection should be considered after preoperative evaluation [IV, B].

2. **Adjuvant Treatment**

For patients with newly diagnosed EC, postsurgical risk stratification and treatment approaches are outlined in Table 4. The 2023 FIGO classification highlights the importance of traditional clinicopathological factors, such as histology, tumor grade, myometrial invasion, and LVSI, but at the same time underlines the role of molecular classifications to predict outcomes [3].

Treatment recommendations by risk category

- **Low Risk**: No adjuvant therapy is recommended due to low recurrence rates [II, A]. Tumors with POLE mutations are also classified as low risk, although data for stage III POLE mutations remain inconclusive. RAINBO POLEmut-Blue is a phase II clinical trial that will assess the safety of de-escalating adjuvant treatment in this population (NCT05255653) [33].
- **Intermediate Risk**: Adjuvant vaginal brachytherapy is the standard treatment [I, A]. The PORTEC-2 trial dem-

Table 4 Treatment recommendations by risk category

Risk category (FIGO 2023)		Treatment
Low risk		
IA1m, ICm	All molecular subgroups	No adjuvant therapy [II, A]
IA2-IA3m	dMMR, NSMP (low-grade and ER pos[a])	
I-IIm[b]	POLEm	
Intermediate risk		
IBm	dMMR, NSMP (low-grade and ERpos)	Adjuvant vaginal BT [I, A] No adjuvant therapy may be considered [III, C]
IIAm	NSMP (low-grade and ERpos)	
IICm	dMMR without cervical stromal invasion and without substantial LVSI	
High-intermediate risk		
IIAm	dMMR	Adjuvant EBRT [II, A]
IIBm	dMMR, NSMP (low-grade and ER pos)	BT can be considered for patients with pN0 lymph node staging [II, B]
IICm	dMMR with cervical stromal invasion and/or substantial LVSI	
High risk		
I-IIIm except IA1m &ICm	NSMP (high-grade or ER neg), p53abn	EBRT with concurrent ChT [I, A], or ChT and sequential RT [I, B]
III-IVA	dMMR[c], NSMP (low-grade and ER pos)	ChT followed by BT can be considered [I, B]

BT, brachytherapy; ChT, chemotherapy; IHC, Immunohistochemistry; ERBT, external beam radiotherapy; ER, estrogen receptor; LSVI, lymphovascular space invasion; m, molecular classification; dMMR, mismatch-repair deficient; NSMP, no specific molecular subtype; RT, radiotherapy

[a]ER positivity defined as ≥ 10% by IHC

[b]POLEm tumors classified as stage III may be considered low risk, although supporting data is currently lacking

[c]The combination of pembrolizumab with ChT (+/− ERBT), followed by maintenance pembrolizumab, may be considered for patients with dMMR EC stage III–IVA [II, B]

onstrated the benefit of brachytherapy ensuring vaginal control with fewer gastrointestinal side effects than external beam radiation therapy (EBRT)[34].

- **High-Intermediate Risk**: For patients with NSMP or dMMR tumors exhibiting cervical stroma invasion without extrauterine extension, or those with substantial LVSI or aggressive histological types, adjuvant radiotherapy is recommended, with EBRT considered standard treatment [II, A]. Brachytherapy could be considered in patients with pN0 staging [II, B].
- **High Risk**: The standard approach is EBRT combined with concurrent chemotherapy (ChT), consisting in two cycles of cisplatin 50 mg/m2 administered the first and fourth weeks, followed by adjuvant ChT (4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m2 (CP) every 3 weeks) [I, A]. The PORTEC-3 trial reported improved overall survival (OS) and progression-free survival (PFS) for the concurrent plus adjuvant ChT group compared to EBRT alone. Subgroup analyses showed that p53abn, stage III and SC benefitted the most [35].
- Additionally, sequential ChT and RT (four cycles of CP administered either before or after RT) could be considered, since a pooled analysis of the ManGO ILIADE-III and NSGO-EC-9501/EORTC-55991 trials demonstrated a benefit with this approach. However, in stage III-IVA EC adding EBRT to ChT with CP showed no improvement in relapse-free survival over CP alone in a phase III trial [I, B] [36]. ChT alone can be also considered based on the GOG-258 trial, that compared ChT (CP) versus ChTRT (concurrent cisplatin with EBRT followed by 4 cycles of CP), in stage III and IV and SC or clear cell stage I-II EC, with no differences in disease free survival (DFS) and OS [I, B] [37].
- Recently, the ENGOT-en11/GOG-3053/KEYNOTE-B21 clinical trial randomized high-risk EC patients to receive pembrolizumab or placebo alongside CP (with or without RT), followed by maintenance pembrolizumab or placebo. The results revealed similar DFS rates between both arms. However, exploratory analyses indicated a benefit for dMMR patients, suggesting that pembrolizumab may be a potential treatment option in combination with ChTRT for these patients [II, B] [38]. The clinical trials RAINBO dMMR-GREEN (NCT05255653) and NRG-GY020 (NCT04214067) aim to confirm the role of immunotherapy (IT) in patients with dMMR EC, comparing RT combined with IT (either durvalumab or pembrolizumab) versus RT alone in two different settings: high-risk and intermediate-high risk disease.

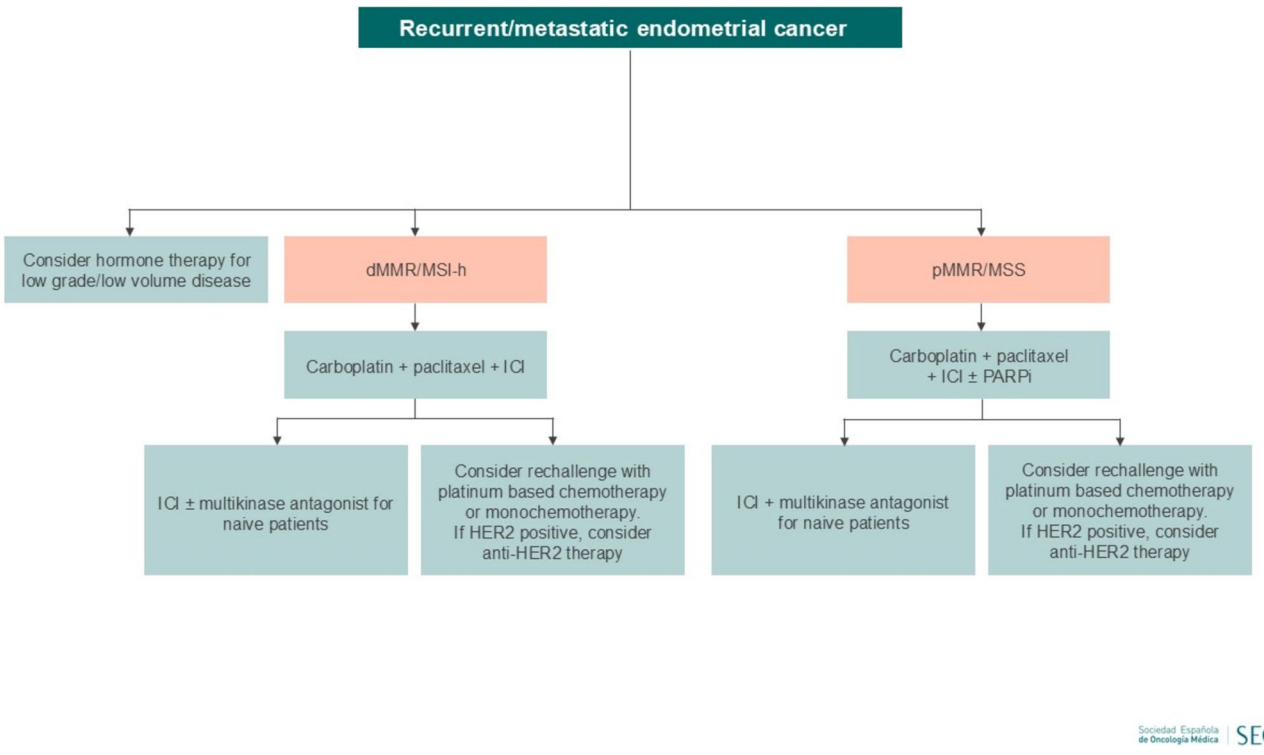

Fig. 1 Algorithm for treatment of advanced disease. dMMR: deficiency MMR; ICI, immune checkpoint inhibitors; MSI-h: microsatellite instability-high; PARPi, poly [ADP-ribose] polymerase inhibitors

Metastatic and recurrent disease

Treatment of metastatic and recurrent disease depends on tumor load, molecular classification and the patient's symptoms and comorbidities. For isolated pelvic recurrence or single metastatic sites, surgical resection, RT [39] or ablative therapy can be considered [IV, A], followed by systemic therapy although its benefit is uncertain [IV, B]. In patients with recurrent unresectable or metastatic disease, ChT, IT and hormonotherapy (HT) are therapeutic options. Enrolment in clinical trials is strongly recommended [V, B] (Fig. 1).

1. First Line

ChT is the treatment of choice. Several combinations have been tested. In the GOG 209 trial, CP was not inferior to cisplatin-doxorubicin-paclitaxel (TAP) with a PFS of 12–14 months and OS of 32 months, and a better toxicity profile for the doublet [40]. Based on these results, the standard ChT treatment for advanced or recurrent EC is the combination of carboplatin (AUC 5–6) and paclitaxel (175 mg/m^2) following a triweekly schedule [I, A].

HT could be an appropriate therapeutic alternative for patients who are low-grade, hormone-receptor positive, without rapidly progressive and/or high-volume metastatic disease [41] [II, A]. Available treatments include progestogens alone (currently the preferred option is megestrol acetate 160 mg QD or medroxyprogesterone acetate 200 mg QD) or combined with tamoxifen, tamoxifen alone, aromatase inhibitors, and fulvestrant [III, A]. Biopsy to confirm hormone-receptor status should be considered at the time of recurrence [IV, B]. The response rate (RR) in ChT-naive patients is about 10–25% [42]. Recently, very promising results have been reported with cyclin-dependent kinase inhibitors 4/6 (CDK4/6) in combination with HT, but these are not yet available outside of clinical trials [43, 44].

- **dMMR population**

The addition of IT to standard ChT has disrupted the first-line treatment of advanced EC. The NRG-GY018 study with pembrolizumab [45] and the RUBY study with dostarlimab [46] evaluated whether concomitant IT with ChT and subsequent maintenance IT improved PFS and/or survival versus ChT alone. Both clinical trials differ in specific aspects of their design and patient populations. Key differences include the time from prior neoadjuvant/adjuvant treatment, duration of IT maintenance, the inclusion or exclusion of carcinosarcoma and other agressive histological types, and the primary endpoint. These differences should be taken into account for optimal treatment decision-making. At the time of publication of this guideline, in the NRG-GY18 study [45], significant differences were achieved in PFS in the dMMR cohort, with medians not reached in the IT arm and 7.6 months (6.4–9.9 months) in the placebo arm (HR 0.3 (95% CI, 019–0.48) and with median OS not reached (HR 0.55 (95% CI, 025–1.19). Similarly, in the RUBY study [46], statistically significant differences were achieved in the dMMR-MSI-h cohort both for PFS and OS (HR = 0.23 [95% CI, 016–0.50] and HR = 0.32 [95% CI, 017–0.63], respectively). Other checkpoint inhibitors have also shown efficacy in the first line of EC (atezolizumab and durvalumab) [47–51]. ChT + IT and IT maintenance (2 years with pembrolizumab or 3 years with dostarlimab) is currently the standard first line treatment for the dMMR population [I, A].

The phase III KEYNOTE-C93 (NCT05173987) and DOMENICA (NCT05201547) studies aim to de-escalate ChT in first line of advanced metastatic treatment in patients with dMMR EC by substituting ChT with IT (either pembrolizumab or dostarlimab). The results of these trials have not yet been published.

- **pMMR population**

In the previously mentioned studies, the population of pMMR patients, comprising various molecular profiles, was also included. In this subgroup, the effectiveness of IT has been demonstrated, although its effect is not as pronounced as in the dMMR population. Thus, ChT + IT is the standard of treatment for pMMR subgroup patients [I, B] [48]. The clinical trial LEAP-001 evaluated the combination of IT (pembrolizumab) with a multikinase antagonist (lenvatinib) versus conventional ChT, without meeting either of its dual primary endpoints (OS and PFS) [49]. Nonetheless, for patients with pMMR relapsed disease after prior chemotherapy in the adjuvant/neoadjuvant setting, the combination of pembrolizumab and lenvatinib may be considered if further ChT is contraindicated [III, C] [52].

Another strategy developed for first-line treatment includes adding poly (ADP ribose) polymerase (PARP) inhibitors to the combination of ChT and IT (RUBY-part 2 study [50] and DUO-E trial [51]). Subgroup analysis suggests a benefit in the pMMR population with the addition of a PARPi to ChT + IT, and thus this approach could be another option for this group of patients [I, B]. Although the combination of PARPi + IO has been approved by the European Medicines Agency, this treatment option will not be reimbursed by the Spanish public health system.

2. **Second and subsequent lines**

- **Patients who have not received treatment with immunotherapy**

For patients who have not received treatment with immunotherapy, checkpoint inhibitors such as pembrolizumab [53, 54] or dostarlimab [55] may be considered. In dMMR patients, a study with dostarlimab (GARNET) showed a RR of 46%, and 90% of patients had not progressed at 12 months in the dMMR cohort [55]. The KEYNOTE-158 study with pembrolizumab in dMMR patients showed a RR of 57% and a non-reached OS and duration of response [53, 54]. In both dMMR and pMMR patients, the results of a phase III study comparing the efficacy and safety of lenvatinib and pembrolizumab versus ChT, following a platinum-based ChT, showed a benefit in PFS (7,3 vs 3,8 months; HR 0,56, 95% CI, 0,48–0,66), OS (18,7 vs 11,9 m; HR 0,65, 95% CI, 0,55–0,77) and RR (33,8 vs 14,7%), regardless of MMR status [52]. However, this combination was associated with a considerable proportion of adverse events, predominantly including hypertension, hypothyroidism, and diarrhea.

For patients with advanced EC and dMMR who have progressed after platinum-based first line ChT, potential treatments include dostarlimab or pembrolizumab alone [III, A], or the combination of pembrolizumab and lenvatinib [I, B]**.** In the pMMR population, the combination of pembrolizumab and lenvatinib is recommended [I, A].

- **Patients who have received treatment with immunotherapy**

In patients who have previously received IT, the choice of a new line of treatment depends on factors including clinical situation, comorbidities, accumulated toxicities, and the presence of biomarkers other than dMMR. Several phase II studies have demonstrated slight activity for drugs such as weekly paclitaxel, docetaxel, oxaliplatin, liposomal adriamycin, topotecan, and ifosfamide. Retreatment with platinum may be considered in patients with late relapses.

Approximately 30% of SC have human epidermal growth factor 2 (HER2) overexpression or amplification, conferring a poorer prognosis. A randomized phase II study [56] demonstrated that adding trastuzumab to CP improved PFS and OS. More recently, the results of the DESTINY-PanTumor02 study with trastuzumab deruxtecan have been reported. Trastuzumab deruxtecan is an antibody–drug conjugate (ADC) containing a humanized IgG1 monoclonal antibody targeting HER2 and an exatecan-derived topoisomerase I inhibitor. Despite being a phase II trial, the RR in the cohort of patients with advanced EC and HER2+++ expression was 84%, with a median PFS of 11.1 months (95% CI 7,1-NR) [57]. In light of these results, the determination of HER2 is recommended due to its therapeutic implications.

The use of antiangiogenic drugs such as bevacizumab as a single agent has shown a RR of 12–15%, which improves in combination with CP, but without demonstrating an advantage regarding PFS or OS in a phase II study [58]. Bevacizumab is not currently approved for advanced EC, although it is still under investigation.

3. **Future directions**

Selinexor has emerged as a promising drug for first-line maintenance of advanced EC or treatment of first relapse. This exportin-1 inhibitor was the drug under evaluation in the SIENDO study [59], a phase III trial in patients with advanced EC randomized to receive maintenance selinexor vs placebo until progression after response to first-line ChT. Its primary endpoint (PFS) was not met, but an exploratory analysis confirmed benefits, especially in the population without a p53 mutation (p53wt). XPORT-EC-042 (NCT05611931) is a phase 3 randomized trial evaluating selinexor's activity in the p53wt population.

In addition, several other ADCs targeting TROP2 (sacituzumab govitecan, sacituzumab tirumotecan, and datopatomab deruxtecan), folate receptor alpha (mirvetuximab, rinatabart sesutecan), and B7H4 (puxitatug samrotecan) are currently under investigation, with very promising results [60].

Follow-up

The primary goal of follow-up in EC is the early detection of recurrent disease. About 50% of patients with a recurrence present with locoregional disease, 25% present with distant recurrence, and the remaining 25% with both [61].

After initial diagnosis and treatment of EC, a follow-up appointment should be scheduled every three to six months for the first two years, and thereafter every six to twelve months, depending on the risk of persistent or recurrent disease [62]. At each follow-up visit, patients should be asked about symptoms of potential recurrence, and a physical exam, including speculum and bimanual pelvic exam, should be performed. All patients should receive counselling on the symptoms of potential recurrence: unexplained vaginal bleeding, detection of a mass, abdominal distension, persistent pain, fatigue, diarrhea, nausea or vomiting, persistent cough, leg swelling, or weight loss.

Serum biomarkers are not recommended, and vaginal cytology is not routinely recommended, as most vaginal recurrences are detected with clinical examination alone [62] [I, A].

There is very little evidence on the benefit of imaging tests as part of EC follow-up. The TOTEM trial, which compares routine hospital visits with a more rigorous follow-up program, is one of the first large, prospective evaluations to address surveillance care in EC [63]. EC patients were included in two different cohorts: 1) low-risk group (FIGO IA G1-2) with a clinical exam every 6 months versus an annual clinical exam, annual vaginal cytology, and CT scan; or 2) high-risk group (IA G3 or ≥ IB) with a clinical exam every 4 months and an annual CT scan, versus a clinical exam and ultrasound every 4 months, and an annual vaginal cytology and CT scan. The relapse rate was 12.3%. No differences in OS were reported. According to the TOTEM trial, a minimalist strategy (clinical examination every 6/12 months for the low-risk group and clinical examination and CT scan every 6/12 months for the high-risk group) could be recommended for the follow-up of EC [I, B].

Despite these results, in high-risk non-endometrioid or FIGO III-IV tumors, imaging may be helpful, with chest/abdominal/pelvic CT recommended every 6 months during the first 3 years, and every 6 to 12 months for 2 additional years [IV, A].

A 2013 meta-analysis of 11 studies supports the use of PET-CT as an accurate method for the evaluation of a suspected recurrence [64].

Most recurrences occur within three years after primary treatment [65]. It seems reasonable for patients to return to annual population-based general physical and pelvic examinations after five years of recurrence-free follow-up [V, B].

Following treatment, EC patients should be counselled on the importance of avoiding obesity and ensuring physical activity and healthy nutrition [66] [IV, A].

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest **SPR** reports Advisory Board, Speaker from GSK; Speaker from MSD, AstraZeneca, Eisai Merck, and Ipsen. **APF** reports Advisory Board, Speaker, Grant, Non-financial Support from Astrazeneca, GSK. Advisory Board, Speaker, Grant from Pharmamar. Advisory Board, Speaker from PharmaAnd, Deciphera and MSD. Advisory Board from Regeneron, Daichii Sankyo and Karyopharm. **MPBG** reports Advisory Board, Speaker from Astra Zeneca, GSK and MSD; Advisory Board and Speaker from Eisai. **ADJF** reports Advisory Board and Speaker from GSK, AstraZeneca, and MSD, and Speaker from EISAI. **LFM** reports Speaker from GSK, Eisai Pharma& AstraZeneca and MSD. **AGM** reports Advisory Board, Speaker from GSK and MSD; Speaker from AstraZeneca and Clovis and Advisory Board from Abbvie and Eisai. **FGM** reports Advisory Board and Speaker from GSK and AstraZeneca; Advisory Board from MSD, Roche, Phamamar and Eisai. **AM** reports Advisory Board and Speaker from AstraZeneca, GSK and MSD; Advisory Board from AbbVie, Eisai and Pharmamar and Speaker from Pharma&. **TMG** has nothing to disclose. **MGM** reports Speaker from MSD, GSK, and AstraZeneca, and Advisory Board from AstraZeneca.

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Informed consent The manuscript does not contain clinical studies or patient data.

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