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SPECIAL ARTICLE

Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Worldwide, endometrial cancer (EC) ranks seventh among all female cancers with the majority of cases occurring between 65 and 75 years of age.[1] In Europe, uterine cancer ranks fourth among female neoplasms, with an incidence of 12.9-20.2:100 000 and a low mortality rate: 2.0-2.7:100 000.[2,3] This discrepancy is due to the fact that 80% of ECs are confined to the uterus at diagnosis and present with postmenopausal bleeding, which leads to prompt detection.[1]

EC is more prevalent in high/intermediate developed countries. Risk factors for EC include body mass index (BMI) (with an increased incidence of +21% for BMI 22-27.2, +43% for BMI 27.5-29-5 and +273% for BMI >30), hypertension, hyperinsulinaemia and prolonged exposure to unopposed estrogen (often related to nulliparity and infertility associated with polycystic ovarian syndrome or tamoxifen use).[4,5]

Mortality rates have been increasing by 1.9% per year on average, mainly attributed to the increasing incidence of obesity, a known risk factor for the most frequent type of EC.[6,7]

ECs have traditionally been classified into two subtypes according to their histopathological characteristics (type 1 and 2).[8] This classification system, however, is in a transition period and is being replaced by a clearly-defined system based on molecular phenotypes.[9]

Although >90% of ECs are sporadic, 5%-10% are hereditary, usually as a part of the hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome. Women with HNPCC have a 10-fold risk of developing EC, as well as an increased risk of colon and ovarian cancer. These are usually microsatellite-unstable tumours and tend to occur at a younger age.[10]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

The traditional dualistic histopathological classification coined by Bokhman split EC into two groups: type I and type II. The endometrioid subtype was categorised as type I, while all other histological subtypes were classified as type II cancers. Type II cancers were associated with a higher risk of relapse compared with type I.[8] Tumours are graded according to the International Federation of Gynecology and Obstetrics (FIGO) defined criteria and are moving towards a two-tier grading combining grade 1 (G1) and grade 2 (G2) endometrioid carcinomas as low grade and grade 3 (G3) as high grade.[11] In addition, multiple factors have been traditionally identified as high risk for recurrent disease: histological subtype, G3 histology, myometrial invasion ≥50%, lymphovascular space invasion (LVSI), lymph node metastases and tumour diameter >2 cm. Substantial LVSI is a major poor prognostic factor. Substantial LVSI is defined

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as widespread invasion of tumour emboli into vascular spaces at and beyond the invasive front of the tumour. Substantial LVSI can be diagnosed on haematoxylin and eosin (H&E) slides without the need for additional immunostains. Although the extent of LVSI may vary per H&E slide, LVSI foci are often found in multiple slides. If the extent of LVSI is limited to fewer than four vessels, it is regarded as focal LVSI. Substantial LVSI is defined as four or more LVSI-positive vessels in at least one H&E slide. In contrast to substantial LVSI, minimal or focal LVSI has limited impact on prognosis.[12-14] Alongside these characteristics, L1 cell adhesion molecule (L1CAM) is another significant indicator of high-risk disease.[15,16] Expression of L1CAM is most frequent in p53-abnormal (p53-abn) tumours but is also predictive of worse outcome among tumours with no specific molecular profile (NSMP).[17,18]

In recent years, it has become increasingly clear that the traditional classification lacks reproducibility and yields heterogenous molecular groups that hamper advances and implementation of precision medicine.[19,20] This is particularly problematic for future clinical trials with targeted approaches that will demand inclusion of cancers with molecular similarities. The EC classification originally proposed by The Cancer Genome Atlas (TCGA) project serves this purpose well, as it is based upon the combination of somatic mutational burden and somatic copy number alterations.[9] This TCGA approach results in the molecular stratification of ECs into four distinct molecular groups; (i) ultramutated [>100 mutations/megabase (mut/Mb)] with pathogenic variations in the exonuclease domain of DNA polymerase epsilon (*POLE)*-ultramutated (*POLE*mut), (ii) hypermutated (10-100 mut/Mb), microsatellite-unstable, (iii) somatic copy number-high with frequent pathogenic variants in *TP53* and (iv) somatic copy number-low with frequently phosphoinositide 3-kinase (PI3K) and WNT signalling abnormalities. Importantly, a range of publications on large and clinically well-annotated (trial) cohorts have shown that surrogate markers can be utilised for a TCGA-inspired molecular classification in routine surgical pathology, without the need for extensive sequencing.[18,21-23] This pragmatic alternative relies on a small number of well-established immunohistochemical (IHC) markers (MSH6, PMS2 and p53) in combination with targeted tumour sequencing (*POLE* hotspot analysis) and also automatically serves to pre-screen for Lynch syndrome as it incorporates reflex testing of the mismatch repair (MMR) proteins (Table 1).

A simple and clearly defined diagnostic algorithm for the molecular EC classification has been proposed[24] (Figure 1). *POLE*mut EC can be diagnosed after the detection of a pathogenic mutation in the exonuclease domain of *POLE*. Guidance about the interpretation of pathogenic variants was recently described by Leon-Castillo et al.,[25] allowing for uniform classification of *POLE*mut EC. Subsequently, for cases that do not carry a pathogenic *POLE* variant, immunostaining of at least two (PMS2 and MSH6) or preferably four (PMS2, MLH1, MSH6 and MSH2) of the MMR proteins is carried out. Complete loss of expression of one or more of these MMR proteins is sufficient for the diagnosis of MMR-deficient (dMMR) EC.[26] Finally, p53 immunostaining serves as a near-perfect surrogate marker for an underlying *TP53* mutation and is, therefore, used to classify EC as p53-abn (after excluding *POLE*mut and dMMR).[27] Extensive study of these surrogate markers has shown a good relationship to clinical outcome, establishing their prognostic value. *POLE*mut EC has an excellent outcome and p53-abn EC has the poorest clinical outcome, independent of risk group, type of adjuvant treatment, tumour type or grade.[21-23] This implies that de-escalation of adjuvant treatment of *POLE*mut EC patients should be explored, as is

Table 1. Molecular and clinicopathological features of endometrial cancer molecular subgroups

	***POLE*mut (i.e. *POLE* EDM)**	**dMMR (i.e. MSI)**	**NSMP (i.e. p53-wt)**	**p53aberrant (i.e. p53-abn, p53-mut)**
Prevalence in TCGA cohort, %	5-15	25-30	30-40	5-15
Associated molecular features	>100 mut/Mb, SCNA-very low, MSS	10-100 mut/Mb, SCNA-low, MSI	<10 mut/Mb, SCNA-low, MSS	<10 mut/Mb, SCNA-high, MSS
Most frequently associated histological features	Endometrioid Often high grade Ambiguous morphology Prominent TILs and TLSs	Endometrioid Often high grade LVSI substantial Prominent TILs MELF-type invasion	Mostly low grade Notable absence of TILs Squamous differentiation ER/PgR diffuse	All histological subtypes Mostly high grade High cytonuclear atypia Low level of TILS
Associated clinical features	Lower BMI Early stage (IA-IB) Early onset	Higher BMI Lynch syndrome	Higher BMI	Lower BMI Advanced stage Late onset
Diagnostic test	NGS/Sanger/Hotspot: P286R, V411L, S297F, A456P, S459F	MMR-IHC: MLH1, MSH2, MSH6, PMS2 MSI assay		p53-IHC Mutant-like/abnormal staining
Prognosis	Excellent	Intermediate	Intermediate Stage-dependent	Poor

Adapted from McAlpine et al.,[119] with permission from John Wiley and Sons.

BMI, body mass index; dMMR, mismatch repair deficient; EDM, exonuclease domain mutation; ER, estrogen receptor; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented type of invasion; MMR-IHC, mismatch repair immunohistochemistry; MSI, microsatellite instability; MSS, microsatellite stable; mut/Mb, mutations/megabase; NGS, next-generation sequencing; NSMP, no specific molecular profile; p53-abn, p53-abnormal; p53-mut, p53-mutant; p53-wt, p53-wild type; PgR, progesterone receptor; *POLE*, polymerase epsilon; *POLE*mut, polymerase epsilon-ultramutated; SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas; TIL, tumour infiltrating lymphocyte; TLS, tertiary lymphoid structure.

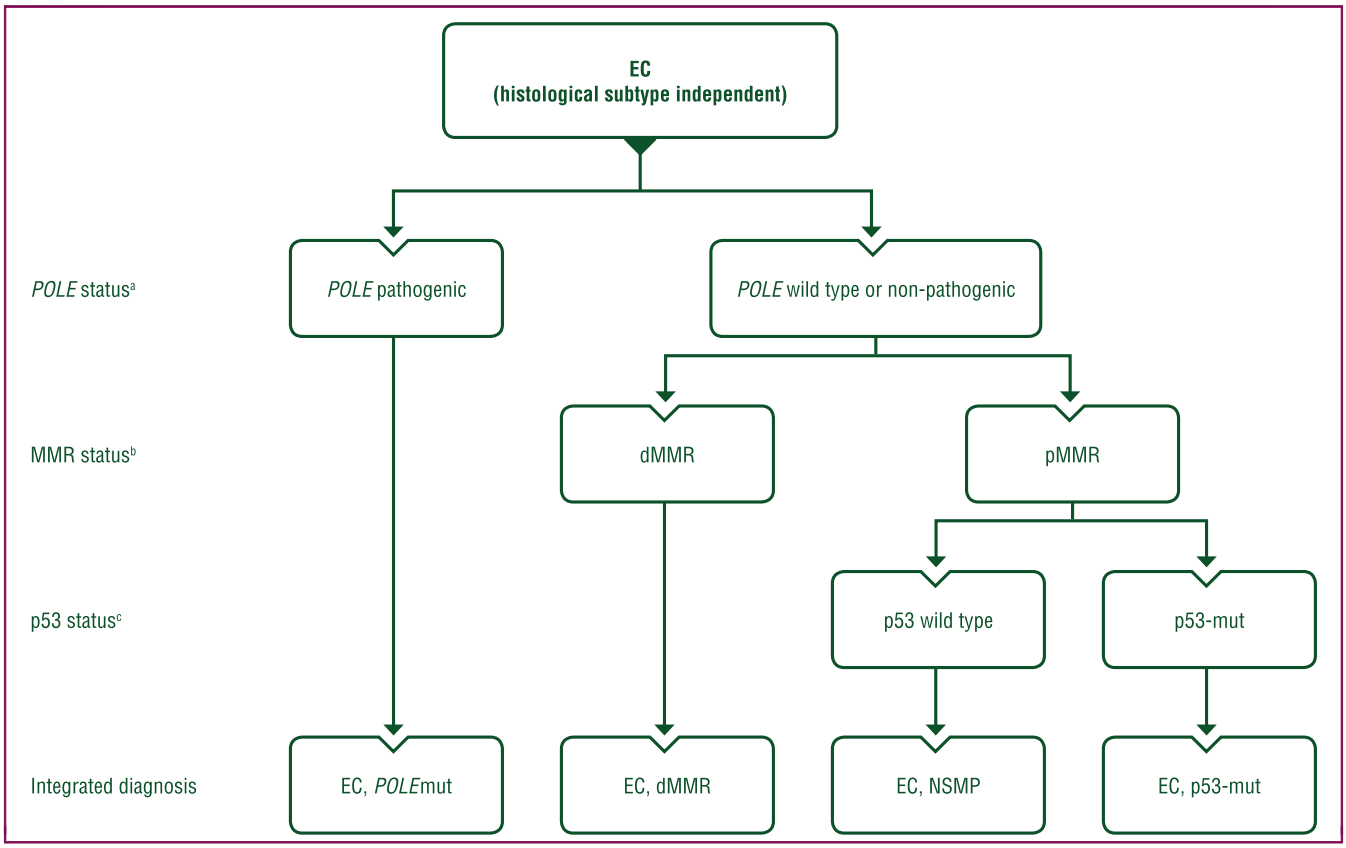

Figure 1. Diagnostic algorithm for the integrated molecular EC classification.
This algorithm can be applied to all histological subtypes of EC (including carcinosarcomas). Please refer to manuscript for further information on *POLE*mut analysis indication.
dMMR, mismatch repair deficient; EC, endometrial cancer; MMR, mismatch repair; NSMP, no specific molecular profile; p53-mut, p53-mutant; pMMR, mismatch repair-proficient; *POLE*, polymerase epsilon; *POLE*mut, polymerase epsilon-ultramutated.
[a]Pathogenic *POLE* variants include p.Pro286Arg, p.Val411Leu, p.Ser297Phe, p.Ala456Pro and p.Ser459Phe.[25]
[b]MMR deficiency is defined by loss of one or more MMR proteins (MLH1, PMS2, MSH2 and MSH6).
[c]p53 immunohistochemistry is an acceptable surrogate marker for *TP53* mutation status in MMR-proficient, *POLE* wild-type EC.[27] Permission to use figure under a Creative Commons CC BY License, Wiley https://www.creativecommons.org/licenses/by-nc-nd/2.0/.[24]

currently being done in the clinical Postoperative Radiation Therapy in Endometrial Cancer (PORTEC)-4a trial.[28] Furthermore, recent data suggest that the greatest benefit for the addition of chemotherapy (ChT) in the adjuvant setting is for those ECs harbouring p53-abn which includes most serous cancers but also a significant portion of other histological subtypes such as carcinosarcomas.[23] This shows how the molecular EC classification has the potential to improve patient management, reducing over- and undertreatment.

In future trial designs, molecular classification should be encouraged as it would allow comparison between groups of patients sharing similar/analagous features.

Molecular classification has been shown to be prognostically enlightening in low-, intermediate- and high-risk EC. Therefore, well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) is now recommended as standard practice for all EC pathology specimens regardless of histological type and to complete the molecular classification following the diagnostic algorithm (Figure 1), by sequencing the exonuclease domain of *POLE* where available. As not all laboratories are currently able to carry out the molecular classification on all ECs, prioritisation of molecular classification should be done for cases where results are relevant to guiding adjuvant treatment recommendations. It applies particularly to those classified as being high grade or at high stage (≥FIGO stage II), as the clinical consequences for these patients will be most pronounced.

In this transition phase, in which two EC classification systems exist, it is recommended that the classification system used is specified. As with other tumour sites undergoing a similar transition, ECs that have not (completely) been molecularly classified should be designated as EC not-otherwise-specified (EC-NOS) and continue the use of the histology-based classification system [e.g. endometrioid-type EC (EEC-NOS)].[24] This additional note will improve clarity for caretakers and patients. The histology-based classification remains unchanged and distinguishes endometrioid, serous, clear-cell and un/dedifferentiated EC. Uterine carcinosarcomas are metaplastic carcinomas with molecular features that overlap with serous and endometrioid adenocarcinomas and, therefore, should be included in this list of 'epithelial endometrial malignancies'. Data on the prognostic and predictive value of the molecular classification for the rarer (non-endometrioid) histological EC

variants are still limited to pilot studies; however, all molecular classes are identified in all histological subtypes.[29,30]

Recommendations

- Histological type, FIGO grade, myometrial invasion and LVSI (focal/substantial) should be described for all EC pathology specimens [V, A].
- Molecular classification through well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) in combination with targeted tumour sequencing (*POLE* hotspot analysis) should be carried out for all EC pathology specimens regardless of histological type [IV, A].

STAGING AND RISK ASSESSMENT

Although EC is a surgically-staged disease according to the FIGO system (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.05.009), preoperative staging may help to establish a recurrence risk group and to define resulting surgical management, mainly on the basis of assessment of myometrial/cervical invasion and lymph node metastases. The preoperative work-up includes clinical and gynaecological examination, transvaginal ultrasound, a full blood count and liver and renal function profiles. Of note, magnetic resonance imaging (MRI) is considered the most accurate imaging technique for preoperative assessment of EC due to its excellent soft tissue contrast resolution. Depth of myometrial invasion and cervical stromal invasion are both important aspects of EC staging. Dynamic contrast-enhanced MRI and T2-weighted images are useful tools in the assessment of these features, with an accuracy of 98% and 90% for assessing myometrial and cervical stromal invasion, respectively.[31] An abdominal and thoracic computed tomography (CT) scan should be considered for investigating the presence of extrapelvic disease. [^{18}F]2-Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET)-CT demonstrates high specificity and positive predictive value for detecting distant metastases.[32] FDG-PET-CT has an excellent diagnostic performance for detecting lymph node metastasis preoperatively and disease recurrence post-operatively in EC patients and can be considered as an additional diagnostic procedure.[33] EC is diagnosed after histopathological examination of samples from dilation and curettage (D&C), or Pipelle biopsy. Hysteroscopy may be helpful to have a representative biopsy or for removal of the target lesion.

Recommendations

- Obtaining endometrial sampling by biopsy or D&C are acceptable initial approaches to histological diagnosis of EC [IV, A].
- The preoperative work-up should include clinical and gynaecological examination, transvaginal ultrasound, pelvic MRI, a full blood count and liver and renal function profiles [IV, B].
- Additional imaging tests (e.g. thoracic and abdominal CT scan and/or FDG-PET-CT) may be considered in those patients at high risk of extrapelvic disease [IV, C].

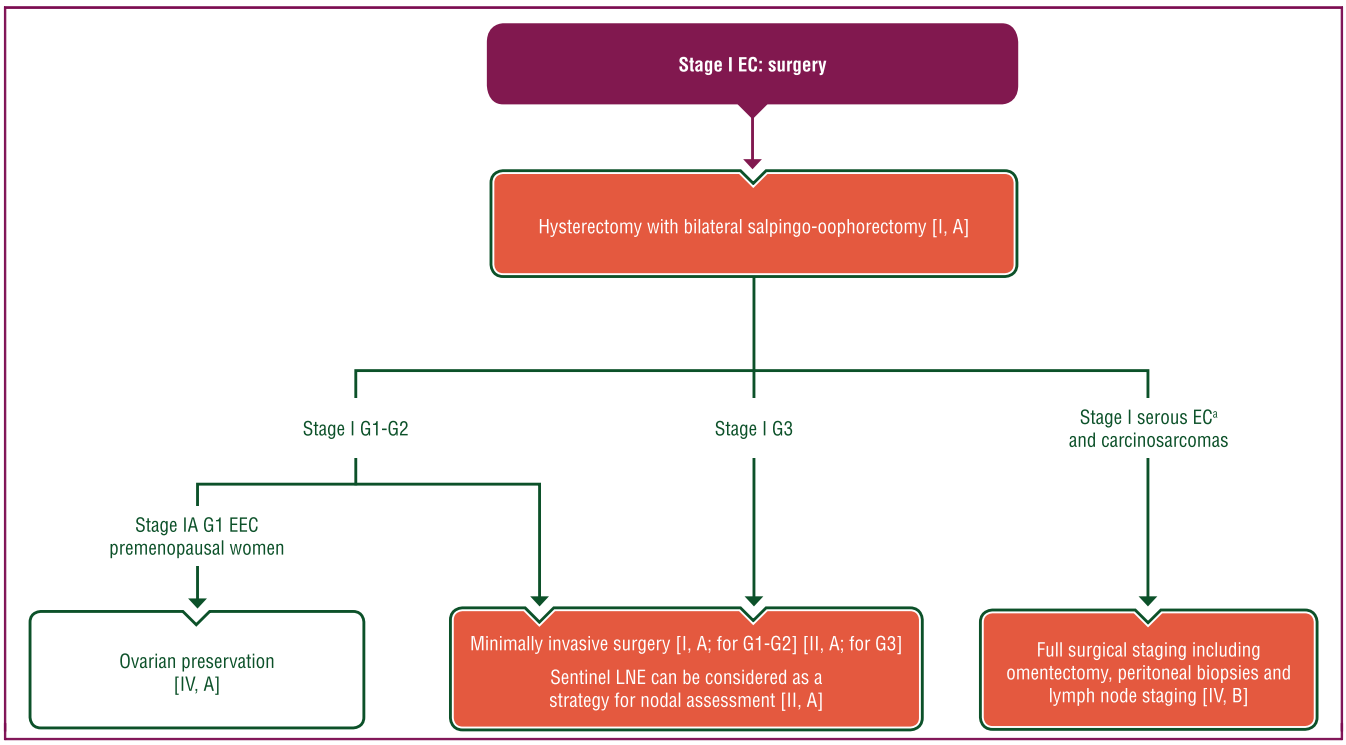

Figure 2. Stage I EC: surgery.
Purple: general categories or stratification; red: surgery; white: other aspects of management.
EC, endometrial cancer; EEC, endometrioid-type endometrial cancer; LNE, lymphadenectomy.
[a]Except in those restricted to polyps.

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Surgery

In early-stage EC, the aim of surgery is to remove macroscopic tumour, examine for microscopic metastases and stage the tumour to assess the need for adjuvant therapy (see Figure 2). Laparotomy has been the traditional surgical approach for the treatment of EC. Large, randomised trials and a meta-analysis have demonstrated that minimally invasive techniques have operative outcomes similar to laparotomy with respect to prognosis.[34,35] Even though the majority of patients included in these trials were low risk (e.g. G1 or G2), with only 17% of patients at higher risk (e.g. defined by G3), the laparoscopic approach can be extended to G3 tumours, since detrimental effects were not demonstrated. A robotic approach is a potential enhancement to standard laparoscopic surgery and may be especially beneficial in obese women. Standard surgery is hysterectomy with bilateral salpingo-oophorectomy. Preservation of ovaries can be considered in premenopausal patients with FIGO stage IA G1 EEC. Ovarian preservation is not recommended for patients at genetic risk for ovarian cancer (e.g. germline *BRCA* mutation, Lynch syndrome). Staging omentectomy should be considered in carcinosarcoma and serous type EC.

The risk of lymph node metastases ranges between $<5\%$ and 40% depending on grade, myometrial invasion and histology. Because the detection of lymph node metastases has an impact on adjuvant therapy, evaluation of lymph node status is recommended in patients with non-endometrioid histology, FIGO IB or G3 disease. Lymph node evaluation could be omitted in endometrioid FIGO IA G1-G2 disease since the risk of nodal metastasis is very low ($<5\%$).[36]

Two prospective randomised trials have investigated the effect of systematic pelvic lymphadenectomy (LNE) in EC.[37,38] These studies have not been able to demonstrate an improvement in prognosis, associated with LNE. Subsequently, multiple reasons were discussed to explain the results, such as the inclusion of patients with low-risk tumours, insufficient surgical quality and imbalance in adjuvant therapy. Therefore, it was concluded that both trials have shown that systematic LNE is not indicated in stage IA G1-G2 endometrioid tumours, but the trials could not provide firm guidance regarding optimal management of patients at a higher risk. The question of systematic LNE is being assessed in the ECLAT trial (NCT03438474).

Sentinel node biopsy or sentinel LNE has emerged as alternative to lymph node dissection for lymph node staging. The sensitivity of sentinel LNE as a lymph node staging approach in early-stage EC patients has been endorsed by multiple studies favouring its implementation in surgical management.[39,40] The FIRES trial, the largest prospective cohort analysing the role of sentinel LNE in stage I EC, has shown that this approach can safely identify sentinel lymph nodes in EC. Currently the only data that support the sentinel LNE in terms of prognosis have been obtained from retrospective studies. Results from randomised clinical trials with a survival endpoint are still lacking. Sentinel LNE with indocyanine green is reported to be feasible and yields the best results from a technical perspective and is therefore the preferred method.[41] Whether a positive pelvic sentinel lymph node evaluation indicates further retroperitoneal staging (pelvic and/or para-aortic LNE) is not yet defined. In conclusion, and based on data provided by prospective and retrospective studies,[39,40] sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It may also represent an alternative to systematic LNE in high-intermediate-risk/high-risk disease stage I-II.

Cytoreductive surgery with the aim of complete resection should be considered in stage III and IV EC (including carcinosarcoma)[42] if feasible and with acceptable morbidity, following full preoperative staging. There seems to be no role for so called suboptimal debulking to residual disease of 1-10 mm like in ovarian cancer.[43]

Adjuvant treatment

The most recently published randomised trials of adjuvant treatment used a long-standing risk-based approach to enrol patients, dependent on stage and pathological features. Recent data, however, suggest that the risk of recurrence needs to take into account the molecular features of the tumour. A molecular classification has been proposed to improve the evaluation of recurrence risk. This is now incorporated into guidelines to aid decision-making regarding adjuvant treatment.

Traditional clinicopathological risk factors, especially age, histopathological type and grade, myometrial invasion and LVSI are important in assessing prognosis. More recently, it has been shown that when LVSI is substantial (also called unequivocal or obvious), there is a greatly increased risk of recurrence and death.[12,44]

As described in the previous sections, TCGA has identified four molecular EC subgroups with significant prognostic differences among them.[9] These clinically relevant molecular subgroups have been replicated using surrogate markers in formalin-fixed, paraffin-embedded tissues, identifying equivalent subgroups: p53-abn, *POLE*mut, dMMR and NSMP.[18,22,45,46] The integration of this molecular classification with the well-established clinicopathological data has resulted in an updated risk classification system to establish the relative risk of recurrence. This system can now be used to explore molecularly-targeted therapy within these subgroups (Table 2).

All recommendations apply to women with FIGO stage I-IVA EC who undergo surgery and do not have any macroscopic residual disease.

Low-risk EC

There is no indication for adjuvant treatment of low-risk EC as the risk of recurrence is low (see Figure 3). Multiple studies have shown no survival benefit from adjuvant treatment and the occasional patient with a local recurrence can effectively be treated with radiotherapy (RT) at

Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; *POLE*mut, polymerase epsilon-ultramutated.

[a]Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.

[b]dMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determining microsatellite instability (i.e. MSI-H).

[c]*POLE*mut stage III might be considered as low risk. Nevertheless, currently there are no data regarding safety of omitting adjuvant therapy.

the time of recurrence.[47-49] Current data from the PORTEC-1/2 studies and additional series have demonstrated the presence of *POLE*mut as an indicator of a favourable EC prognosis, independent of other clinicopathological variables. Hence, patients with stage I-II tumours and a *POLE*mut are now also considered to be low risk and unlikely to benefit from adjuvant treatment.[18,45,50,51] *POLE*mut EC, however, comprises only a small subgroup (overall 5%-15% of EC) and it is infrequent to find this mutation in patients with advanced disease.[18,23] Nevertheless, omitting adjuvant treatment is also an option among stage III *POLE*mut EC patients, although there are currently no available outcome data without adjuvant treatment. Clinical studies (observational) are strongly encouraged[52,53] in this *POLE*mut EC group.

Intermediate-risk EC

Both PORTEC-1 and Gynaecology Oncology Group (GOG)-99 clinical trials demonstrated that pelvic RT significantly reduced locoregional recurrence in the intermediate-risk group, with the largest absolute reductions in the designated high-intermediate-risk groups.[47,48] As the majority of recurrences for those cases were in the vaginal vault, PORTEC-2 evaluated the efficacy and toxicity of vaginal brachytherapy (VBT) compared with external beam RT (EBRT) in the PORTEC-1 defined high-intermediate group (see Figure 3). Ten-year survival data confirmed excellent vaginal control rates (>96%) in both arms, with similar rates of isolated pelvic recurrence, distant metastasis and overall survival (OS).[53-55] Moreover, in this long-term analysis, substantial LVSI, p53-abn and L1CAM overexpression were all strongly associated with a higher risk of recurrence. Among those patients with any of these unfavourable risk factors, EBRT provided a better control than VBT. Therefore, patients with any of these features are no longer classified as intermediate risk.[18,19,55]

A Danish population study confirmed that the risk of locoregional relapse was higher (~14%) with omission of VBT, but the OS was no different due to successful treatment of relapse.[56] According to these data, the omission of adjuvant treatment may be considered in individualised cases following patient counselling.

Within this intermediate group are those patients with stage IA non-endometrioid and/or p53-abn cancers without myometrial invasion and no or focal LVSI. It should be noted that these patients were not included in the randomised trials. Therefore, the potential benefit of adjuvant therapy for those patients is unclear; consequently, the recommendation for adjuvant treatment or observation should be considered on a case-by-case basis following multidisciplinary discussion.

High-intermediate-risk EC

The traditional high-intermediate-risk EC group, defined in both PORTEC-1 and GOG-99 (e.g. age 70 years or older with one uterine risk factor, age 50 years or older with two uterine risk factors or age 18 years or older with three uterine risk factors: uterine risk factors include G2 or G3 tumour, outer-half depth of invasion and lymphovascular invasion) has been modified due to further knowledge regarding molecular and clinicopathological characteristics.[18,55] This re-defined group, as described in Table 2, comprises a group with a higher risk of recurrence. Hence, the potential benefit of ChT to decrease disease recurrence in this EC group has been addressed in several trials, none of which included exactly the same risk population. Two of these studies, both published more than a decade ago, evaluated adjuvant platinum-based ChT versus RT and found no OS advantage.[57,58] The pooled analysis of the ManGO ILIADE-III trial and NSGO-EC-9501/EORTC-55991 trial comparing RT with RT plus ChT showed that although progression-free survival (PFS) was improved with

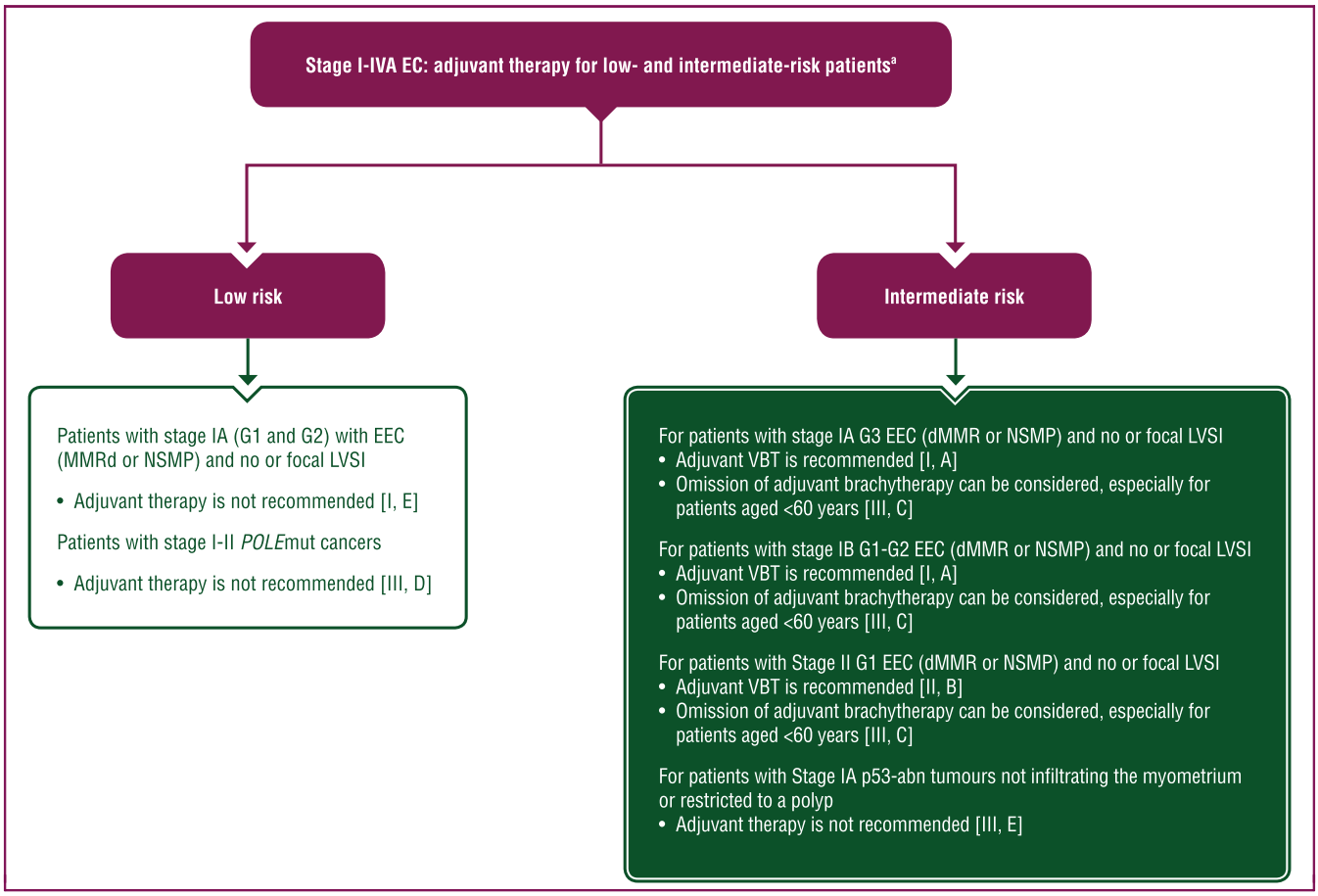

Figure 3. Stage I-IVA EC: adjuvant therapy for low- and intermediate-risk patients.
Purple: general categories or stratification; green: RT; white: other aspects of management. Further therapeutic options are described in the manuscript.
dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid-type endometrial cancer; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; *POLE*mut, polymerase epsilon-ultramutated; RT radiotherapy; VBT, vaginal brachytherapy.
[a]If completely resected without residual disease.

combined therapy, the OS trend did not reach statistical significance.[59] Recently, the phase III trial GOG-249 analysed the impact on recurrence-free survival (RFS) of substituting pelvic RT for VBT followed by three cycles of paclitaxel and carboplatin in patients with high-intermediate-risk EC. The trial enrolled women meeting GOG-99 high-intermediate-risk criteria and/or stage II or stage I-II serous or clear-cell carcinoma. Remarkably, 89% had LNE and were node-negative. The 5-year RFS and OS showed no differences between both arms. Acute adverse events of grade $\geq$2 were found in 94% of patients receiving ChT and VBT versus 44% of those assigned to RT. At 24 months, sensory neuropathy of grade $\geq$2 was significantly worse in the ChT/VBT arm at 10% versus $<$1% with RT. Although the assessment of long-term side-effects would need a longer follow-up, these results have led the authors to conclude that pelvic RT remained the appropriate standard treatment of high-risk early-stage disease.[60]

Moreover, the recent PORTEC-3 trial provides further data to define better treatment approaches.[61,62] This trial evaluated the role of ChT during and after RT (CRT) versus pelvic RT alone in women with high-intermediate-risk and high-risk EC (stage IA G3 with LVSI; stage IB G3; stage II of any grade; stage III endometrioid and stage IA-III uterine serous or clear-cell carcinoma). Of note, about half of patients had high-risk early-stage disease (including 28% G3 and 25% non-endometrioid EC), and 45% had stage III disease. The recently published update with a median follow-up of 72.6 months did show a significant improvement in 5-year OS and failure-free survival (FFS). When analysing results by stage, combined adjuvant treatment of those women with stage I-II non-serous cancers showed only a small absolute improvement (i.e. 2% in 5-year OS and 4% in FFS). In consequence, taking the results of the GOG-249 and PORTEC-3 trials together, the decision of combined treatment in these early stages should be discussed on a case-by-case basis, considering the balance between the increased frequency of adverse events and the outcome benefit (see Figure 4).

High-risk EC

The adoption of a precise definition of high-risk EC has been challenging. Currently, stage III-IVA EC without residual disease or stage I-IVA p53-abn or non-endometrioid carcinomas without residual disease with myometrial invasion are all considered high-risk EC.

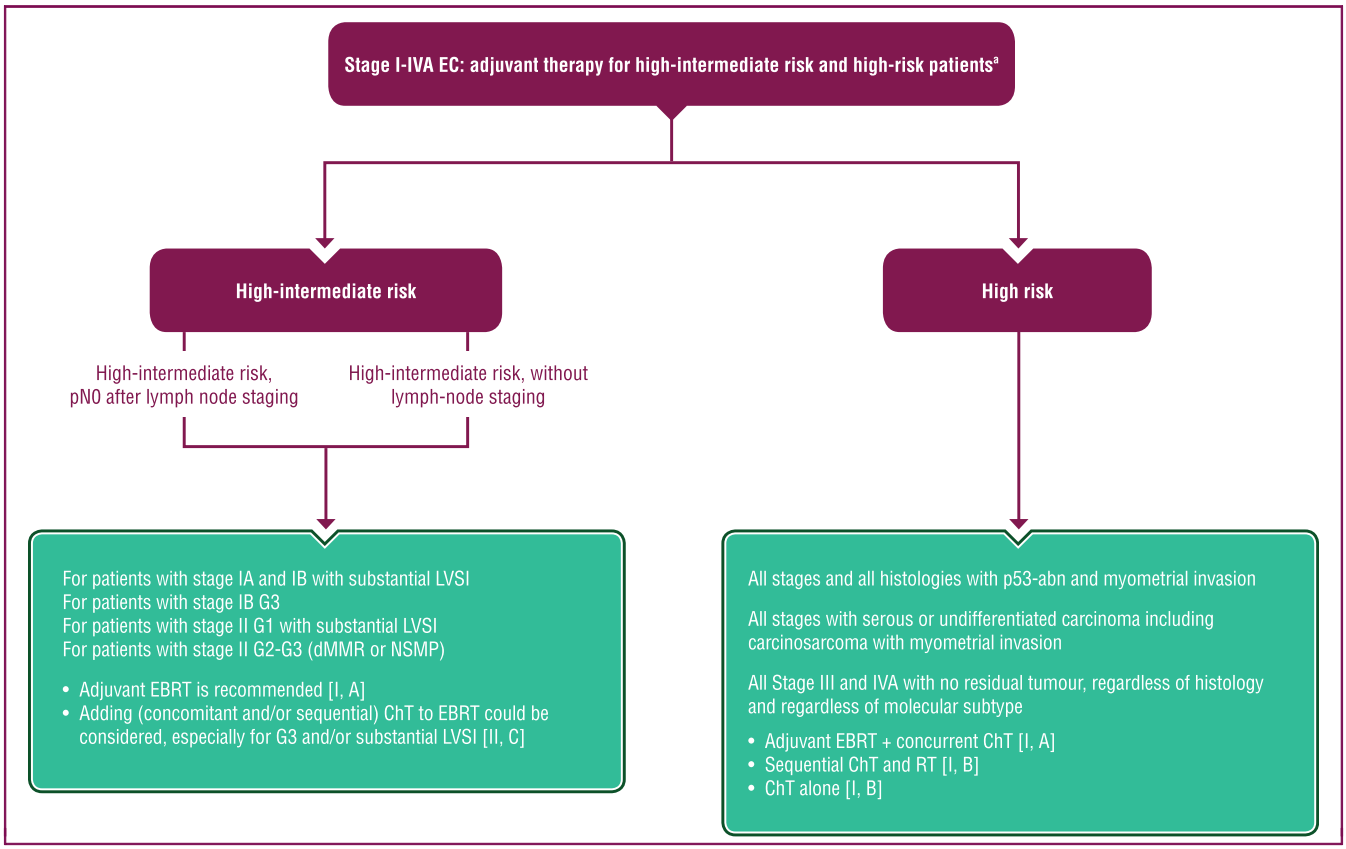

Figure 4. Stage I-IVA EC: adjuvant therapy for intermediate- and high-risk patients.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments. Further therapeutic options are described in the manuscript.
ChT, chemotherapy; dMMR, mismatch repair deficient; EBRT, external beam radiotherapy; EC, endometrial cancer; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; RT, radiotherapy.
[a]If completely resected without residual disease.

The recent data from three relevant phase III trials (PORTEC-3, GOG-249 and GOG-258), enrolling high-intermediate-risk and high-risk EC patients, two of which were described in the previous section, are leading to a shift in the treatment paradigm.

Updated analysis of PORTEC-3, with a median follow-up of 72 months, showed a 5% OS benefit and a 7% benefit in FFS in the concurrent plus adjuvant ChT group, compared with RT alone. In the subgroup analysis, women with stage III EC along with those of serous histology obtained the greatest benefit of adding ChT to RT. Of note, only 105 patients with serous cancer were enrolled in PORTEC-3; thus, the number of women and events are too low to report on treatment efficacy across the different stages.[61] Traditionally, clear-cell and serous cancers have been merged due to their worse prognosis. Nevertheless, in this PORTEC-3 analysis, the frequency of recurrence among women with clear-cell cancers (especially p53 wild type) was similar to that of women with endometrioid tumours and markedly lower than that of women with serous cancers.

In terms of safety profile, the addition of ChT resulted in significantly higher treatment-related toxicity, but most differences resolved from 12 months onwards, with persisting differences in long-term G2 sensory neuropathy.

In the GOG-258 trial, 813 women with stage III-IVA EC were randomised to receive pelvic RT with concurrent and adjuvant ChT (same regimen as the PORTEC-3 trial) or to receive ChT alone (six cycles of carboplatin and paclitaxel). Although no differences in RFS and OS were found, significantly more vaginal and pelvic and/or para-aortic recurrences were seen in women treated with ChT alone.[63] Taking into consideration the results from these two trials, the benefit obtained by adding ChT to RT and the resulting toxicity rate increase should be discussed as part of shared decision making between doctors and their patients. While CRT is the recommended regimen for high-risk patients, RT alone may be recommended in cases of major comorbidities and contraindications to ChT.[61]

Given the strong emerging prognostic value of the EC molecular classification, the outcome and impact of ChT for each molecular subgroup was analysed using the tissue samples from PORTEC-3. The results showed that patients with p53-abn EC had the poorest prognosis regardless of histology, whereas *POLE*mut was the strongest favourable prognostic factor, even among high-grade and advance-stage cases. The treatment effect was also different within the molecular subgroups. Patients with p53-abn EC had a highly significant benefit from CRT regardless of the

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histological subtype and stage, whereas patients with *POLE*mut EC had an excellent survival in both treatment arms.

Patients with dMMR and NSMP EC, however, had an intermediate outcome and when the differences in adjuvant treatment effect (CRT versus RT) were analysed among these molecular subgroups, no benefit was observed between CRT and RT alone in patients with dMMR EC. Patients with NSMP EC had a trend toward benefit from CRT, similar to the overall trial outcome.[23]

Carcinosarcomas, which are currently considered metaplastic dedifferentiated ECs, have not been included in the trials cited above. They are uniformly regarded as high risk and most are classified as p53-abn EC. Recommendations for high-risk disease are largely applicable to carcinosarcomas as well and this histology should be included in the upcoming clinical trials.[64]

Recommendations

- Hysterectomy with bilateral salpingo-oophorectomy is the standard surgical procedure in early-stage EC [I, A].
- Minimally invasive surgery is the recommended approach in stage I G1-G2 EC [I, A].
- Minimally invasive surgery may also be the preferred surgical approach in stage I G3 [II, A].
- Ovarian preservation can be considered in premenopausal women with stage IA G1 EEC [IV, A].
- Sentinel LNE can be considered as a strategy for nodal assessment in low-risk/intermediate-risk EC (e.g. stage IA G1-G3 and stage IB G1-G2) [II, A]. It can be omitted in cases without myometrial invasion. Systematic LNE is not recommended in this group [II, D].
- Surgical lymph node staging should be carried out in patients with high-intermediate-risk/high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic LNE for lymph node staging in high-intermediate-risk/high-risk stage I-II [III, B].
- Full surgical staging including omentectomy, peritoneal biopsies and lymph node staging should be considered in serous ECs and carcinosarcomas [IV, B].
- When feasible, and with acceptable morbidity, cytoreductive surgery to a maximal surgical extent should be considered in stage III and IV [IV, B].

Low-risk EC

- For patients with stage IA (G1 and G2) with endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant treatment is not recommended [I, E].
- For patients with stage IA non-endometrioid type (and/or p53-abn), without myometrial invasion and no or focal LVSI, adjuvant treatment is not recommended [III, E].
- For patients with stage I-II *POLE*mut cancers adjuvant treatment is not recommended [III, D].
- For patients with stage III *POLE*mut cancers, treatment within the scope of clinical trials is recommended but no adjuvant treatment is also an option [III, C].

Intermediate-risk EC

- For patients with stage IA G3 endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence [I, A].
- For patients with stage IB G1-G2 endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence [I, A].
- For patients with stage II G1 endometrioid cancer (dMMR and NSMP) and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence [II, B].
- Omission of adjuvant VBT can be considered (especially for patients aged $<$60 years) for all above stages, after patient counselling and with appropriate follow-up [III, C].

High-intermediate-risk EC with lymph node staging (pN0).

- For patients with stage IA and IB with substantial LVSI, stage IB G3, stage II G1 with substantial LVSI and stage II G2-G3 (dMMR and NSMP):
  - Adjuvant EBRT is recommended [I, A].
  - Adding (concomitant and/or sequential) ChT to EBRT could be considered, especially for G3 and/or substantial LVSI [II, C].
  - Adjuvant VBT (instead of EBRT) could be recommended to decrease vaginal recurrence, especially for those without substantial LVSI [II, C].
  - With close follow-up, omission of any adjuvant treatment is an option following shared decision making with the patient [IV, C].

High-intermediate-risk EC without lymph node staging.

- For patients with stage IA and IB with substantial LVSI, stage IB G3, stage II G1 with substantial LVSI and stage II G2-G3 (dMMR and NSMP):
  - Adjuvant EBRT is recommended [I, A].
  - Adding (concomitant and/or sequential) ChT to EBRT could be considered especially for substantial LVSI and G3 [II, C].
  - Adjuvant VBT could be considered for IB G3 without substantial LVSI to decrease vaginal recurrence [II, C].

HIGH-RISK EC

- Adjuvant EBRT with concurrent and adjuvant ChT is recommended [I, A].
- Sequential ChT and RT can be used [I, C].
- ChT alone is an alternative option [I, B].

RECURRENT/METASTATIC DISEASE

Outcomes of advanced/recurrent disease remain poor, with 5-year OS rates of 20%-25%.[65] The treatment of patients with recurrent/metastatic EC should always require a multidisciplinary approach in specialised centres and should be guided by the patient's condition, extent of the disease, prior therapies and molecular profile. Important prognostic factors impacting local control and survival in recurrent EC

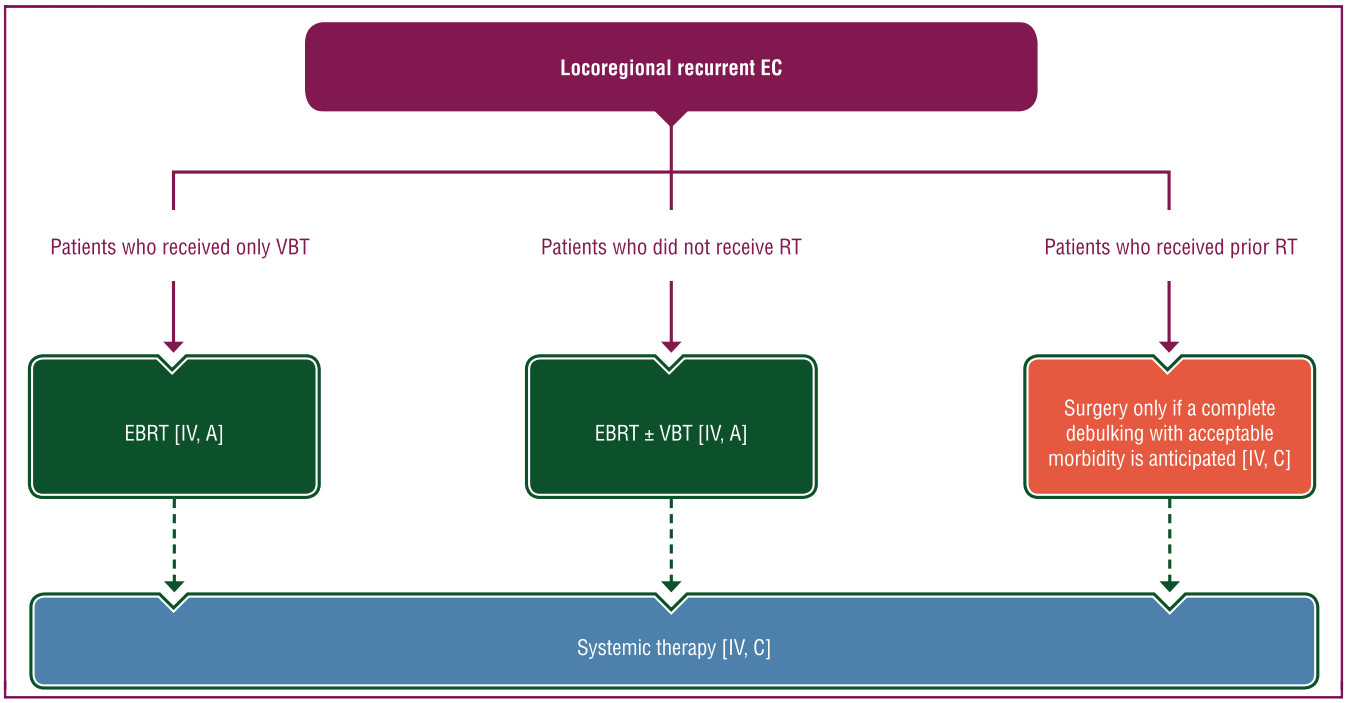

Figure 5. Locoregional recurrent EC.
Purple: general categories or stratification; red: surgery; green: RT; blue: systemic anticancer therapy.
Optional ----▸
EBRT, external beam radiotherapy; EC, endometrial cancer; RT radiotherapy; VBT, vaginal brachytherapy.

include both site(s) and extension of the recurrence (e.g. isolated vaginal, pelvic; peritoneal carcinomatosis), tumour size ($\leq$2 cm versus $>$2 cm), prior RT, relapse-free interval and histology. Indeed, a longer relapse-free interval, low-grade histology, isolated vaginal recurrence and endometrioid histology are associated with a longer survival (see Figure 5).[66,67]

RT

Patients with recurrent EC following primary surgical procedure alone may be appropriate candidates for RT, with salvage RT being the recommendation of choice in RT-naive patients with local or locoregional recurrence. Prognosis with isolated vaginal recurrence is more favourable compared with pelvic nodal recurrence.[47] For selected patients with small vaginal recurrences who have not received prior RT, RT may be curative.

The use of primary RT influences sites of recurrence and survival after relapse. As shown in PORTEC-1, survival is longer for patients with recurrent disease not previously treated with RT in the adjuvant setting.[47,68] After an isolated vaginal recurrence, the 5-year survival rate for the non-irradiated group was 65%, compared with 43% for patients randomised to the adjuvant RT arm of PORTEC-1. Vaginal recurrences can be successfully treated with RT, with 5-year OS of 33%-84% and a 5-year disease-specific survival of 51%-77%,[68-72] with a combination of RT plus VBT providing the best outcomes.[73]

Rates of pelvic-limited recurrences vary from 4.9% at 8 years in low-risk disease[47] to 26% at 3 years in high-risk disease. For patients with a pelvic recurrence, the 3-year survival rate is 8%, compared with 73% for those with isolated vaginal recurrences.[47,68] This survival rate is comparable to the 3-year survival rate for patients with distant metastatic disease.[47,68] Considering that the poor prognosis associated with pelvic recurrence mainly comprises high-risk distant failures, combining salvage RT with systemic therapy could improve the therapeutic gain of salvage RT.

Surgery

RT is the treatment of choice in previously non-irradiated patients with isolated vaginal or locoregional recurrence.[74] For patients with recurrent disease who received prior RT, including resectable peritoneal and lymph node relapses, surgery should be considered only if complete resection of macroscopic disease appears feasible with an acceptable morbidity.[75] To date, and acknowledging the limitations of data from retrospective studies, the only factor associated with an improved OS is achievement of complete debulking. Moreover, radical surgery procedure with the intention of this complete resection should be considered in specialised centres after excluding distant metastasis. Pelvic exenteration may be considered for central local relapse.[76] The role of complementary ChT after surgery for recurrence is not well established due to the lack of studies that have properly addressed this approach. In addition, various retrospective series have shown conflicting results. Hence, the indication for ChT should be evaluated on an individualised basis.[67,75,77] Surgery may also be an option in cases with oligometastatic disease (defined as a state of limited, one to five metastatic tumours) for which local ablative therapy could be a radical approach.[78] Discussion of the cases in a

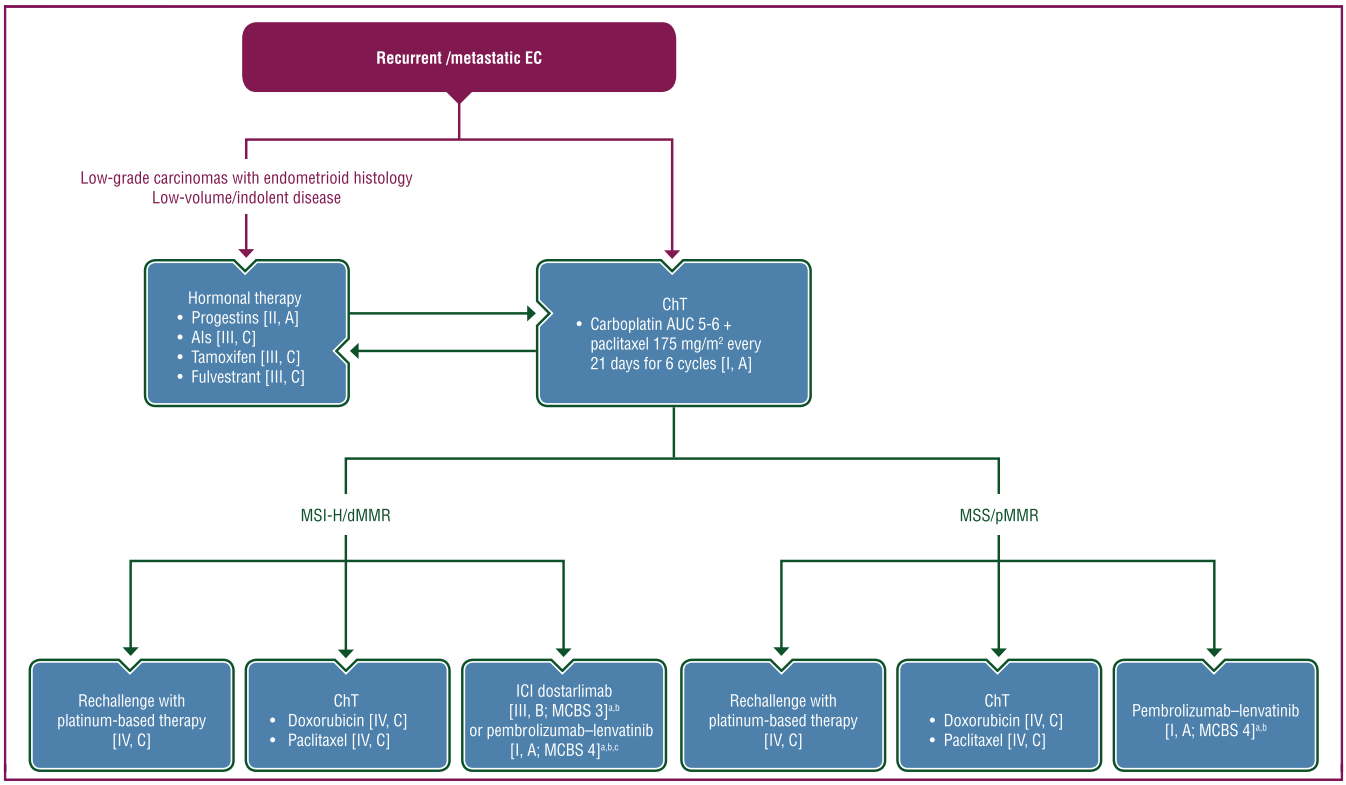

Figure 6. Metastatic EC.
Purple: general categories or stratification; blue: systemic anticancer therapy.
AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; dMMR, mismatch repair deficient; EC, endometrial cancer; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient.
[a]In patients eligible for further treatment after failure of platinum-based therapy.
[b]ESMO-MCBS v1.1[116] was used to calculate scores for new therapies/indications approved by the European Medicines Agency or Food and Drug Administration (FDA). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]FDA approval is restricted to patients whose tumours are not MSI-H or dMMR.

multidisciplinary setting is critical to develop individualised treatment plans and to communicate potential side-effects and expected outcomes (see Figure 6).

Systemic therapy

For relapsed disease not amenable to surgery and/or RT, the standard approach remains ChT or hormonal therapy (see Figure 6). Currently, and following the results of GOG-209, carboplatin AUC 5-6 plus paclitaxel 175 mg/m^2 every 21 days for six cycles should be considered the first-line therapy for advanced or recurrent EC. In this phase III trial, paclitaxel—carboplatin was not inferior to the cisplatin—doxorubicin—paclitaxel (TAP) regimen with regard to efficacy [overall response rate (ORR) of 40%-50%; median PFS and OS of 14 and 32 months, respectively] and was associated with a more favourable toxicity profile.[79] The combination of carboplatin—paclitaxel with antiangiogenic agent bevacizumab failed to demonstrate a clear benefit with PFS [10.5 versus 13.7 months; hazard ratio (HR) 0.84, $P = 0.43$] and OS (29.7 versus 40.0 months; HR 0.71, $P = 0.24$) with respect to standard of care.[80] ChT treatment options beyond first-line therapy are limited with no standard of care identified. Palliative options, such as taxanes and doxorubicin, display moderate activity (ORR of 20%).[81-83]

As mimicking the ovarian cancer treatment approach, the concept of 'platinum-sensitivity and re-treatment with platinum' has been investigated in several retrospective studies in the setting of recurrent EC. These studies have shown that platinum-based ChT re-challenge may be considered an option for selected patients who relapse >6 months since last platinum-based ChT.[84,85]

Hormonal therapy has formerly been accepted as first-line therapy for advanced EC, and given its safety profile and mode of administration, is still an attractive therapeutic option for a select group of patients.[81,82] Factors reported to be predictive of response to endocrine therapy include low-grade endometrioid histology and, to a less clear extent, the status of estrogen receptor (ER)/progesterone receptor (PgR). While higher levels of ER and PgR expression are clearly associated with better outcomes in diseases such as breast cancer, the predictive value of ER/PgR in EC is confounded by both a lack of standardisation in tissue processing and clear cut-off limits. It is possible, however, to infer an association between ER/PgR status and response rates to endocrine therapy, with higher responses in ER/PgR-positive tumours. Having said this, responses have also been reported in ER/PgR-negative tumours.[86] Moreover, due to reported differences in ER/PgR status between primary and recurrent disease, the optimal timing and selection of tissue for determining receptor status

remains an unresolved issue. The standard agents for treatment of patients with recurrent EC are progestins. A recent summary analysis of progestins used as first-line therapy for metastatic/recurrent EC found an ORR of 23.3%, a median PFS of 2.9 months and a median OS of 9.2 months.[87] Alternative options include, tamoxifen, fulvestrant and aromatase inhibitors (AIs). In the recent PARAGON trial, anastrozole showed a clinical benefit rate of 44%, with 7% overall responses.[88]

Immune checkpoint blockade monotherapy in advanced EC. Given that ∼30% of primary ECs are microsatellite instability-high/dMMR (MSI-H/dMMR), indicating immune dysregulation, immune checkpoint blockade (ICB) therapy has been explored both as monotherapy and in combination with cytotoxic ChT, other immunotherapy or targeted agents. A pivotal therapeutic advance was the Food and Drug Administration (FDA) accelerated approval of pembrolizumab [anti-programmed cell death protein 1 (PD-1)] for the treatment of advanced MSI-H or dMMR solid tumours. This marked the first approval of a tumour-agnostic, histology-independent cancer therapy in which treatment is based on a common tumour biomarker rather than the anatomical location of origin. The KEYNOTE-158 trial of pembrolizumab across 27 advanced MSI-H/dMMR solid tumours confirmed the activity on EC population and identified the presence of tumour mutational burden-high (TMB-H) biomarker [defined as ≥10 mut/Mb] as a predictor of response to pembrolizumab.[89] These data led to accelerated FDA approval for pembrolizumab for the treatment of TMB-H solid tumours (as determined by the FoundationOne CDx assay) that have progressed following prior therapy, including EC. Other anti-PD-1/programmed death-ligand 1 (PD-L1) agents that have shown encouraging activity in dMMR EC include avelumab,[90] durvalumab[91] and dostarlimab.[92] The activity and safety of dostarlimab were analysed in the GARNET trial. This ongoing phase Ib study has enrolled 104 patients with dMMR EC. Of these, 71 had measurable disease at baseline and ≥6 months follow-up and were included in the primary analysis. The confirmed ORR was 42.3% (a confirmed complete or partial response was seen in 12.7% patients and 29.6%, respectively). The median duration of response was not reached (median follow-up was 11.2 months). In light of these results, on 22 and 23 April 2021, both the FDA and the European Medicines Agency (EMA), respectively, approved dostarlimab as monotherapy for the treatment of adult patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen (see Figure 6). Objective responses have also been observed with atezolizumab (anti-PD-L1) and nivolumab in PD-L1-positive EC.[93]

ICB and antiangiogenic targeted agents. The FDA, Australian Therapeutic Goods Administration and Health Canada recently granted accelerated approval to the combination of the oral multikinase inhibitor lenvatinib (targets vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor-α, RET and KIT) in combination with pembrolizumab for the treatment of advanced EC that is not MSI-H or dMMR after platinum-based ChT.[94] This was based on KEYNOTE 146, a phase Ib/II study of lenvatinib plus pembrolizumab in select solid tumours including EC (NCT02501096). In the final efficacy analysis, among 108 previously treated patients, the ORR was 38% at week 24 per investigator review per immune-related RECIST with median PFS and OS of 7.5 and 16.7 months, respectively. The ORR in the MMR-proficient (pMMR) ($n = 94$) and dMMR ($n = 11$) cohorts were 36% and 64%, respectively, and responses were seen regardless of MSI status, PD-L1 status or histology.[94] Treatment-emergent adverse events, notably hypertension, fatigue and diarrhoea, were common and overall dose reductions or interruptions occurred in 65% and 72% patients, respectively.

The results from the phase III trial (KEYNOTE-775-NCT03517449) were presented at the Society of Gynaecologic Oncology virtual meeting in March 2021. The combination of pembrolizumab and lenvatinib led to a statistically significant improvement in OS (HR 0.62, 95% CI 0.51-0.75, $P < 0.0001$), PFS (HR 0.56, 95% CI 0.47-0.66, $P < 0.0001$) and ORR (31.9% versus 14.7%) compared with standard ChT in patients with previously treated advanced EC, therefore meeting its dual primary endpoints and key secondary endpoint.[95] In addition, this combination is under investigation as first-line therapy versus carboplatin and paclitaxel ChT in advanced EC (NCT03884101). In light of these results, on 21 July 2021, the FDA approved pembrolizumab in combination with lenvatinib for patients with advanced EC that is neither MSI-H nor dMMR, and who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or RT. In addition, on 20 January 2022, the EMA approved the same regimen, pembrolizumab in combination with lenvatinib, for the treatment of advanced or recurrent EC in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting, regardless of MMR status and who are not candidates for curative surgery or RT (see Figure 6).[96]

Targeted therapy approaches. The cyclin-dependent kinases (CDKs) are a family of serine—threonine kinases involved in cell-cycle progression. In preclinical and clinical studies, palbociclib, a selective inhibitor of the CDKs, CDK4 and CDK6, has been shown to reverse endocrine resistance and inhibit the growth of ER-positive breast cancer cells synergistically with antiestrogens, and the combination of letrozole and palbociclib has been approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[97] Interim results of the phase II ENGOT EN3 PALEO trial in previously treated endometrioid EC tumours that were ER-positive showed that letrozole plus palbociclib significantly improved PFS compared with letrozole plus placebo: median 8.3 versus 3.0 months, respectively; (HR 0.56, 95% CI 0.32-0.98, $P = 0.041$).[98]

The PI3K pathway is one of the most frequently pathogenically activated pathways in EC, and is pivotal in proliferation, survival, metastasis, metabolism and angiogenesis.[99] Several

phase II studies investigating PI3K inhibitors both as monotherapy and in combination in recurrent EC have demonstrated ORR ranging from 4% to 32%. Despite the promising efficacy observed with these combinations, their safety profiles have compromised their further development.[100] In the GOG-86P randomised phase II study, recurrent/metastatic EC patients were allocated to three different arms: carboplatin—paclitaxel—temsirolimus, paclitaxel—carboplatin—bevacizumab and ixabepilone—carboplatin—bevacizumab. The trial failed to show a significant PFS difference with respect to historical control, namely the carboplatin—paclitaxel arm of trial GOG209.[101]

The *HER2 (ERBB2)* gene is amplified in 17%-33% of uterine carcinosarcomas and serous carcinomas.[102,103] A small randomised phase II trial of carboplatin—paclitaxel with or without trastuzumab in HER2/neu-positive serous EC showed an increase in both PFS and OS for those receiving trastuzumab.[104]

Adavosertib, a WEE1 inhibitor, reported 29.4% ORR and 38.2% clinical benefit in a population of 34 heavily pretreated serous EC patients.[105] This promising preliminary activity warrants further investigation.

Future directions. Numerous ICB combination strategies with targeted therapies, other immunotherapeutic agents, ChT and RT are currently ongoing and have the potential to alter the EC treatment landscape.

Recommendations

- For patients with locoregional recurrence following primary surgery alone, the preferred primary therapy should be RT with VBT [IV, A].
- Adding systemic therapy to salvage RT could be considered [IV, C].
- For patients with recurrent disease following RT, surgery should be considered only if a complete debulking with acceptable morbidity is anticipated [IV, C].
- Complementary systemic therapy after surgery could be considered [IV, C].
- The first-line standard ChT treatment is carboplatin AUC 5-6 plus paclitaxel 175 mg/m^2 every 21 days for six cycles [I, A].
- Hormone therapy could be considered as front-line systemic therapy for patients with low-grade carcinomas endometrioid histology [III, A].
- Progestins (medroxyprogesterone acetate 200 mg and megestrol acetate 160 mg) are the recommended agents [II, A].
- Other options for hormonal therapies include AIs, tamoxifen and fulvestrant [III, C].
- There is no standard of care for second-line ChT. Doxorubicin and weekly paclitaxel are considered the most active therapies [IV, C].
- ICB monotherapy could be considered after platinum-based therapy failure in patients with MSI-H/dMMR EC [III, B].
- Dostarlimab has recently been approved by both the EMA and the FDA for this indication [III, B; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3].
- Pembrolizumab is FDA approved for the treatment of TMB-H solid tumours (as determined by the FoundationOne CDx assay) that have progressed following prior therapy for EC [III, B; ESMO-MCBS v1.1 score: 3; not EMA approved].
- Pembrolizumab—lenvatinib is approved by the EMA for EC patients who have failed a previous platinum-based ChT, and who are not candidates for curative surgery or RT. FDA approval is for EC patients whose tumours are not dMMR/MSI-H [I, A; ESMO-MCBS v1.1 score: 4].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

With >80% of patients diagnosed in the early stages of the disease and an excellent prognosis (5-year survival rate >95% for stage I), a large number of patients with EC will be long-term survivors. Awareness and management of the long-term effects of EC and its treatment are important.

Surveillance of recurrence

Most EC recurrences occur within 3 years of initial treatment and in most recurrences are associated with symptoms. Therefore, the probability of detecting a relapse during a planned follow-up consultation among asymptomatic patients is quite low.[106-108] There is no evidence from randomised studies for the role of intensive doctor-led, hospital-based surveillance in EC follow-up evaluation and no consensus on what testing should be utilised.[109] Therefore, medical surveillance can be adjusted to risk factors.

For low-risk groups, the suggested frequency of follow-up is every 6 months with physical and gynaecological examination for the first 2 years, and then yearly until 5 years; in this group of patients, phone follow-up can be an alternative.[110] Patient education regarding concerning signs and symptoms is a critical component of post-treatment care. In the high-risk groups, physical and gynaecological examinations are recommended every 3 months for the first 3 years, and then every 6 months until 5 years. As CT scans detect only 15% of recurrences, routine use is not advocated. Nevertheless, it could be considered in the high-risk group, particularly if there was node extension (e.g. every 6 months the first 3 years and then on an individual basis). PET-CT has been shown to be more sensitive and specific for the assessment of suspected recurrent EC; however, its use in routine follow-up has not been well studied[111] and its indication must be individualised. The sensitivity and the specificity of cancer antigen 125 in EC are low and routine determination during follow-up is not recommended. Finally, it should be noted that Pap smears have not been useful for detecting local recurrences.

Long-term side-effects and promotion of healthy life

In addition to evaluation of recurrence, patients should be encouraged to continue with recommended cancer screening programmes for breast and colorectal cancers and follow-up of comorbidities. EC patients suffer from different

comorbidities mainly linked with age and obesity with higher risk of long-term cardiovascular events.[112]

The main long-term symptoms reported by the patients are fatigue, psychosocial distress, sexuality and gynaeco-urinary disorders, chronic pain, lymphoedema and neuropathy (if ChT). Obesity is associated with low quality of life and physical function.[113] Lifestyle interventions may improve fatigue, physical functioning and result in weight loss and psycho-educational programmes could improve mood disorders and sexuality complaints.[114] Therefore, promotion of regular exercise, healthy diet and weight management should be addressed with all EC survivors.

Limited data are available on hormone replacement therapy, so the decision must be discussed with the patients who experience menopausal symptoms on the basis of benefit/risk.[115]

Recommendations

- For low-risk EC, the proposed surveillance is every 6 months, with physical and gynaecological examination for the first 2 years and then yearly until 5 years [V, C].
- In the low-risk group, phone follow-up can be an alternative to hospital-based follow-up consultation [II, B].
- For the high-risk groups, physical and gynaecological examinations are recommended every 3 months for the first 3 years, and then every 6 months until 5 years [V, C].
- A CT scan or PET-CT could be considered in the high-risk group, particularly if node extension was present [V, D].
- Regular exercise, healthy diet and weight management should be promoted with all EC survivors [II, B].

METHODOLOGY

This Clinical Practice Guideline was developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.05.009. ESMO-MCBS v1.1[116] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this Clinical Practice Guideline. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.05.009.[117,118] Statements without grading were considered justified standard clinical practice by the authors. Future updates to this Clinical Practice Guideline will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/gynaecological-cancers/endometrial-cancer.

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