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Letter to the Editor

Adjuvant treatment algorithm based on recent ESGO/ESTRO/ESP guidelines for early endometrial carcinoma according to prognostic risk groups

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ABSTRACT

The incidence of endometrial cancer (EC) is unfortunately increasing. Often diagnosis is made at an early stage and surgery is the curative treatment. Nevertheless, adjuvant treatment is proposed to reduce the risk of relapse. This treatment is tailored based on the extent of the disease, such as the presence of distant metastasis, the extent of involvement of adjacent organs or lymph nodes. However, histological parameters such as myometrial invasion, substantial lymphovascular space invasion, invasion of the cervical stroma or tumor grade are also key to selecting adjuvant treatment. The Cancer Genome Atlas (TCGA) project has demonstrated the superiority of molecular classification over histological evaluation in EC to determine the prognosis. The International Federation of Gynecology and Obstetrics 2023 staging for EC is the first staging system that has incorporated molecular biomarkers on top of morpho-histological classification. Currently, all patients should have a molecular profile of their tumor and a lymph node assessment. The landmark treatment of stage I–III ECs is surgery followed by radiotherapy. The European guidelines updated in 2025 has divided EC in 4 risk categories with specific adjuvant treatment. For clinicians, it is seen as a complex landscape from surveillance to chemo-radiotherapy. Therefore, we propose here a practical pocket guideline for adjuvant treatment of early-stage EC patients based on a review of the different clinical trials in the adjuvant setting and on existing guidelines. This pocket guideline may also serve as a base for incorporation of new clinical trials under the RAINBO umbrella research program.

Keywords: Endometrial Cancer; Radiotherapy; Immunotherapy; Chemotherapy

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Conflict of Interest

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REQUIRMENTS TO TAILOR ADJUVANT TREATMENT OF ENDOMETRIAL CANCER (EC) PATIENTS

The new guidelines presented in 2025 by European Society of Gynecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) in various congresses refine adjuvant treatment for early-stage EC patients. But it is a complex landscape from surveillance to chemoradiotherapy. Adjuvant treatment must be adapted based on risk factors that are histological characteristics, molecular profiles and clinical stage. Until today, our adjuvant treatment decision was based solely on TNM staging, grade and histological subtype. The International Federation of Gynecology and Obstetrics (FIGO) 2023 classification (**Fig. S1**) has improved the definition of lymph node invasion (micro or macro metastases, pelvic and/or para-aortic involvement), and has introduced selective management for more aggressive histological subtypes (high grade carcinoma, serous carcinoma, clear cell carcinoma, carcinosarcoma or mesonephric-like carcinoma). A major and unique feature of the new FIGO staging is the incorporation of molecular classification [1]. The Cancer Genome Atlas (TCGA) highlighted the prognostic superiority of molecular classification over histological evaluation, especially in the context of high-grade endometrioid carcinoma. Since then, the Proactive Molecular Risk Classifier for Endometrial Cancer classifier is used in routine clinical practice as a cost effective and reliable surrogate to TCGA classification [2]. Therefore, the guidelines published previously by ESGO, ESTRO, and ESP, have divided early stages ECs into 4 different risk groups based on the combination of all known prognostic factors [3]. A pocket memo has already been published to help in the definition of prognostic risk groups [4]. ESGO has also developed a mobile app. We propose here a practical pocket guideline for adjuvant treatment of early-stage EC patients based on their molecular phenotype and other risk factors (**Fig. 1**). Currently, all patients should have a molecular profile of their tumor and a lymph node status assessment, since these 2 elements are the most important to define the risk of relapse of early-stage EC patients. Retroperitoneal staging is under debate, as 2 old trials have failed to demonstrate an overall survival benefit of the addition lymphadenectomy over simple hysterectomy, but these trials included too many low-risk patients [5]. Modern prospective trials or retrospective studies have highlighted the importance of pelvic and para-aortic

<table>
<tr><td></td><td colspan="10">Molecular classification</td></tr>
<tr><td rowspan="3">Stage
FIGO 2023</td><td rowspan="3">POLEmut</td><td colspan="5">MMRd</td><td colspan="3">p53wt</td><td colspan="2">NSMP</td><td rowspan="3">p53abn</td></tr>
<tr><td colspan="3">LG</td><td colspan="2">HG</td><td colspan="3">LG & ER pos</td><td>LG & ER neg</td><td>HG</td></tr>
<tr><td>LVSI– & MYO–</td><td>LVSI– & MYO+</td><td>LVSI+ or Cervix+</td><td>LVSI– or Cervix–</td><td>LVSI+ or Cervix–</td><td>MYO– & Cervix–</td><td>MYO+ & Cervix+</td><td>LVSI+</td><td></td><td></td></tr>
<tr><td>IA1 & IC</td><td colspan="10">No treatment</td></tr>
<tr><td>I</td><td rowspan="3">No treatment or inclusion in RAINBO Blue†</td><td>No treatment</td><td>VBT*</td><td>EBRT</td><td>VBT*</td><td>CRT or inclusion in RAINBO Green</td><td>No treatment</td><td>VBT*</td><td>EBRT</td><td rowspan="3">CRT</td><td rowspan="3">CRT or inclusion in RAINBO Orange if ER+</td><td rowspan="3">Chemo +/– radiotherapy or inclusion in RAINBO Red with VBT if parameter, vagina or margins positive</td></tr>
<tr><td>II</td></tr>
<tr><td>III–IVA</td><td colspan="5">Chemo-Immuno</td><td colspan="3">CRT</td></tr>
</table>

Fig. 1. Adjuvant treatment algorithm for early-stage endometrial cancer. Treatment decision is based on clinical stage using FIGO 2023 and molecular classification. Moreover, some histological features are also taken into account such as tumor grade (LG and HG), presence of myometrial invasion (MYO– and MYO+), infiltration of the cervix (cervix+) and presence of LVSI (LVSI+ and LVSI–). Boxes representing risk categories have been colored; in blue: low-risk; green: intermediate risk; orange: high-intermediate risk and in purple: high-risk. Text is also colored in order to represent biomolecular subtypes based on ProMiseE; in blue: POLEMut; green: MMRd; orange: NSMP Low-grade and ER+; purple: NSMP; red: p53abnormal/high copy number and in black: non-endometrioid. Following treatments are possible; VBT, EBRT, CRT, Chemo-Immuno.
Chemo-Immuno, chemotherapy and immunotherapy; CRT, chemoradiotherapy; EBRT, external beam radiotherapy; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; HG, high or grade 3; LG, low or grade 1–2; LVSI, lymphovascular space invasion; LVSI+, presence of tumor cells >5 lymphovascular spaces, multifocal or diffuse; LVSI–, negative LVSI or ≤5 around the tumor; MMRd, mismatch repair deficient; MYO–, without myometrial invasion; MYO+, with myometrial invasion; VBT, vaginal brachytherapy.
*Consider no treatment if patient younger than 60 years.
†POLE mut stage IVA can't be included in RAINBO Blue and should receive chemotherapy and radiotherapy.

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lymphadenectomy, despite an increased risk of surgical complications [6]. Moreover, subanalysis of PORTEC-3 have nicely showed that the prognostic significance of molecular group is less distinct when patients with lymph node involvement are excluded [7]. Sentinel node biopsy (SLNB) could replace lymphadenectomy and has been accepted for use for low-risk patients, but remains controversial in patients at intermediate to high-risk. Several high-quality retrospective studies comparing hysterectomy with SLNB versus lymphadenectomy have shown no difference in survival outcomes, but a better outcome in terms of surgical complications. Importantly, no further lymph node relapses were observed, but all studies confirmed the prognostic importance of lymph node involvement [8]. Before performing SLNB on all our EC patients, we should await the results of randomized trials such as ALICE, ENDO-3, and SELECT in intermediate-high and high-risk patients. If the lymph node assessment is not possible, which is a very rare situation in the area of the sentinel node protocol, then it should be considered as Nx and has no impact on clinical staging.

ADJUVANT TREATMENT OF LOW-RISK EC PATIENTS

Low-risk patients have a relapse risk below 8%. Most of them are stage I–II *POLEmut* EC patients. Of note, not all *POLE* mutations are associated with an ultramutated phenotype, only mutations arising in exons 9–14 and 19 [9]. Retrospective analyses of several randomized trials suggest that there is no benefit for an adjuvant treatment in stage I–II POLE-ultramutated group of patients. In order to gather prospective datas, we propose to include those patients in the registrational RAINBO Blue Trial. For stage III–IVA EC patients, there is currently no data supporting the use of adjuvant chemotherapy. One question remaining is the real added value of radiotherapy. Therefore, we recommend the inclusion of stage III patients in RAINBO Blue where the omission of radiotherapy is an option according to institutional guidelines. In resected stage IVA, one may still consider adjuvant radiotherapy. Based on PORTEC, Swedish and Danish studies [10-13], stage IA1 and IC EC patients irrespective of the molecular subtypes are also low-risk. The last group of patients are those with low-grade mismatch repair deficient (MMRd) EC patients without lymphovascular space invasion (LVSI) and myometrial invasion (MYO), or those with low-grade ER positive NSMP EC patients without LVSI and infiltration of the cervix. All of them don't require adjuvant treatment.

ADJUVANT TREATMENT OF INTERMEDIATE RISK EC PATIENTS

Intermediate risk patients have a risk of relapse between 8% and 15% mostly localized on the vaginal vault. PORTEC-1 trial has demonstrated that adjuvant radiotherapy significantly reduces the risk of loco-regional relapse without improving overall survival [10]. PORTEC-2 have demonstrated that vaginal brachytherapy (VBT) offers the same vaginal control and survival rate as external beam radiotherapy (EBRT) for intermediate risk patients [11]. The health-related quality of life was better in the group of patients treated with VBT. Therefore, we recommend to perform only adjuvant VBT for all stage I–II MMRd and low-grade ER+ NSMPS EC patients if they have no LVSI nor infiltration of the cervix, since these characteristics are predictive for pelvic recurrences. Low-grade patients should have MYO, otherwise they don't need adjuvant treatment. We will recommend omission of adjuvant treatment in all intermediate-risk patients if they are younger than 60 years based on PORTEC, Swedish and Danish studies [10-13]. Most of the patients included in these

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randomized trials are MMRd and NSMP endometrioid carcinomas with an intermediate-risk group profile. Therefore, this recommendation is solid and applicable for most EC patients.

ADJUVANT TREATMENT OF HIGH-INTERMEDIATE RISK EC PATIENTS

High-Intermediate risk group is a very heterogenous category. They share a higher risk of pelvic or para-aortic nodal recurrence and also distant metastases between 15% to 25%. PORTEC-3 and GOG-258 studies have demonstrated that while radiotherapy prevents pelvic recurrence, it is chemotherapy that prevents distant metastases [14,15]. Based on these 2 trials, EBRT should be given to all high-intermediate risk patients with the addition of chemotherapy. One should, however, question whether the slight improvement of efficacy outweighs the toxicity of this combination. In a subanalysis of PORTEC-3, it is suggested that there is no benefit of additional chemotherapy in the group of MMRd/hypermutated carcinomas [16]. Therefore, we propose based on recent guidelines to perform only EBRT in low-grade MMRd stage I/II patients with LVSI and infiltration of the cervix to decrease the risk of local relapse. For high-grade MMRd stage I/II patients with LVSI and infiltration of the cervix, we suggest adding chemotherapy. For high-grade MMRd stage I/II EC patients, we should also consider the place of immunotherapy with immune checkpoint inhibitors. The recently published ENGOT-en11 trial has evaluated the benefit of adding an immunotherapy, pembrolizumab, an anti-programmed cell death protein 1 antibody, on top of a chemotherapy, with or without radiotherapy in newly diagnosed, high-risk EC patients [17]. Amongst the 141 MMRd patients randomized in the experimental arm, only 8 patients (6%) relapsed (hazard ratio=0.31). This magnitude of benefit is equal to the one observed in first-line metastatic setting, suggesting that immunotherapy must be given as early as possible to those patients. Therefore, we propose to include all stage I/II high grade MMRd EC with LVSI and infiltration of the cervix in the RAINBO Green Trial evaluating the addition of immunotherapy during chemotherapy and radiotherapy but also as maintenance treatment for 1 year.

ADJUVANT TREATMENT OF HIGH-RISK EC PATIENTS

High-risk patients have a risk above 25% of presenting relapses mainly systemic metastases. This group of patients consist of all non-POLE mutated patients with a stage III or stage IVA and also stage I/II abnormal p53 and NSMP who aren't low grade and ER positive. A recent new analysis of the TransPORTEC Consortium has showed that these 2 groups of patients have the worst outcome [18]. Therefore, they must receive the combination of chemotherapy and EBRT. In PORTEC-3 study, they received either EBRT alone or EBRT with 2 cycles of cisplatine followed by 4 cycles carboplatine-paclitaxel [14]. With a median follow-up of 72 months, there is an increase of 5% of overall survival at 5 years in favor of the combination arm. The biggest benefit is seen in stage III carcinomas and in serous carcinomas regardless of stage. GOG-258 trial uses the same chemo-radiotherapy regimen of PORTEC-3 but with 6 courses of chemotherapy before EBRT versus chemotherapy alone [13]. In this study an overlapping benefit is seen. Therefore, for all those patients, a chemo-radiotherapy must be proposed. Despite this treatment, nearly half of the patients will relapse within the first 5 years and die of their cancer. Therefore, new treatment options must be provided. The addition of immunotherapy has failed to improve outcome as shown

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in the ENGOT-en11 trial except in the MMRd subgroup of patients [17]. We recommend as an option chemotherapy alone in stage III–IV MMRd patients with the addition of immunotherapy. The p53 abnormal / high copy number EC share some molecular characteristics with ovarian cancers (OC). PARP inhibitors have improved the prognosis of OC patients. The DUO-E trial demonstrates that olaparib, a PARP inhibitor, on top of chemo-immunotherapy, improved the survival of EC in first-line metastatic setting [19]. So, we endorse to test PARP inhibitors in the adjuvant setting. Therefore, we propose to include high-risk patients with p53 abnl EC in the RAINBO Red Trial evaluating the benefit of PARP inhibitors as maintenance therapy. We recommend as an option chemotherapy alone in stage III–IV p53 abnormal patients. For NSMP low-grade ER negative and high-grade (a new molecular subtype) since they are at high-risk of relapse, we recommend a chemo-radiotherapy. Of note, high grade NSMP ER positive EC patients could be included in the RAINBO Orange Trial that evaluates the replacement of chemotherapy by hormonotherapy on top of radiotherapy. Carcinosarcomas should be treated as high-risk carcinomas and not as sarcomas. Finally, in the future or already today, we should consider avoiding surgery as first treatment in stage III–IVA EC and starting instead with chemo-immunotherapy, based on recent trials published in the metastatic setting.

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SUPPLEMENTARY MATERIAL

Fig. S1
International Federation of Gynecology and Obstetrics 2023 classification for endometrial cancer.

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