Review

Adjuvant treatment in endometrial cancer: when and what to choose

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Abstract

Endometrial cancer is the most common gynecological malignancy in developed countries. The management is primarily surgical, but adjuvant treatment may be indicated after surgery, according to the risk of recurrence. This review will focus on the prognostic risk groups presented in the 2020 ESGO/ESTRO/ESP guidelines and the ongoing trials based on new molecular markers that will help to get a more personalized cancer medicine.

Keywords: Endometrial carcinoma; Adjuvant treatment; Molecular markers; Risk factors

1. Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries, resulting in the sixth most diagnosed cancer in women worldwide, with 417,000 new cases and 97,000 deaths in 2020 [1]. Most of cases are diagnosed at early stages and usually affect postmenopausal women. The management is primarily surgical, with the standard treatment consisting of hysterectomy and bilateral salpingo-oophorectomy completed with pelvic and para-aortic lymphadenectomy or sentinel lymph node biopsy [2].

In 1983, Bokhman described two types of endometrial cancer (EC). The first pathogenetic type (type 1) is the most common (70–80%) and is usually characterized by a favorable prognosis, often presenting with localized disease confined to the uterus. It is usually diagnosed in women with obesity, signs of hyperestrogenism, hyperlipidemia, and consists of low-grade, endometrioid, hormone-receptor-positive tumors that are well or moderately differentiated. Type 2 tumors (20–30%), in contrast, are more common in non-obese women, usually have non-endometrioid histology, such as serous, clear-cell, undifferentiated carcinomas or carcinosarcomas, are high-grade and hormone receptor-negative, associated with a poor prognosis because the high risk of metastasis [3].

2. Recommendations for adjuvant treatment in EC

Prognosis in EC is strictly related to the stage of the disease at diagnosis: the 5-year survival rate in stage I and II EC is 80–90% and becomes less than 25% in stage III and IV [4].

Adjuvant treatment recommendations are based on the risk of disease relapse established for each patient. The overall risk of recurrence is estimated as 13% regardless of the stage, and 3% for patients in the low-risk group. Ap-

Table 1. Clinicopathological risk factors in endometrial cancer.

- Patient's age
- Stage of disease (FIGO 2009)
- Depth of myometrial invasion
- Grade of differentiation
- Histotype
- Lymphovascular space invasion (LVSI)

proximately 70% of all recurrences are symptomatic and occur within the first 3 years of follow-up [5].

In the ESMO/ESGO/ESTRO consensus conference on EC published in 2016, five risk groups (low, intermediate, high-intermediate, high and advanced/metastatic) have been proposed to guide adjuvant therapy, according to clinicopathological risk factors (see Table 1) [6].

Overall, adjuvant treatments adapted to the clinicopathological risk factors achieve excellent outcomes if we consider the group of type I EC in early stage, and most patients have a good prognosis and are cured with local treatments. However, these guidelines had some limitations to predict the effective patient's outcome. Studies have noticed that many patients with good prognostic elements experience relapses and will eventually show poor survival. Conversely, some patients that are usually treated because of unfavorable prognostic factors will never experience recurrences.

Based only on clinicopathological prognostic risk factors, the choice of adjuvant treatment seems to lead to overtreatment in some cases, to undertreatment in others [7,8]. Identifying the subset of tumors with an effective high risk of relapse became a real issue, having significant implications for surgical staging planning and adjuvant treatment decisions.

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This review will focus on the new prognostic risk groups presented in the 2020 ESGO/ESTRO/ESP guidelines, underlining the impact of the new molecular classification. We will also discuss the ongoing trials and new perspectives that will probably change the choice of adjuvant treatment in EC patients.

3. The new molecular characterization for EC

In 2013, The Cancer Genome Atlas (TCGA) Research Network performed an integrated genomic and proteomic analysis of 373 ECs, showing that these tumors can be reclassified in four new molecular prognostic groups: ultra-mutated tumors, with a very high mutational rate; hypermutated tumors, with high mutational rate and microsatellite-instability (MSI); copy-number low tumors, with low mutational rate and low somatic copy number alterations; copy-number high tumors, characterized by high somatic copy number alterations rate [8].

The outcome was significantly different between the four molecular subtypes: DNA polymerase epsilon-mutated (*POLE*mut) tumors had best prognosis, with 100% of progression-free survival after 5 years, whereas copy-number high tumors had the poorest outcome, with about 50% of progression-free survival after 5 years. MSI and copy-number low tumors seemed to have an intermediate prognosis [8].

However, these new molecular classes require performing a copy-number analysis, a tumor DNA sequencing that is complex and costly, not feasible in routine clinical practice. For this reason, the Vancouver group developed a molecular classification system that is more economic, simple, faster and usable in daily clinical practice. This molecular classification, named ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer), uses surrogate prognostic markers based on immunohistochemisrty (IHC) for mismatch repair (MMR) proteins and p53, and *POLE* exonuclease domain hotspot sequencing [9]. IHC stains for MMR and p53 are universally available in laboratories; *POLE* hotspot sequencing needs to be implemented in a clinical setting.

Studies have demonstrated that ProMisE can also be assessed on endometrial biopsy. Moreover, there is a strong a highly favorable concordance between diagnostic endometrial specimens and final hysterectomy samples, with also a strong interlaboratory agreement. These can be crucial factors in decision making regarding a patient care [10,11].

3.1 POLEmut group

Polymerase Epsilon synthesizes the forward strand during conventional DNA synthesis and is responsible for the usually low mutation rate in eukaryotic DNA replication. Pathogenetic mutations in the exonuclease domain of the *POLE* gene cause the development of genomic in-

stability and an ultra-mutated tumor phenotype with low somatic copy-number alterations [12,13]. Tumors with a pathogenic *POLE* mutation have a high number of tumor-infiltrating lymphocytes and programmed death-ligand 1 (PD-L1) receptors expressed on cancer cells [7]. This group includes 6–9.6% of EC [7,8,14–17], it is more common in earlier stages of disease and can be frequent in high-grade endometrioid EC, where it has been found in 15–22% of cases, according to different series [18]. The prognosis for patients with this molecular profile is excellent [19].

3.2 Mismatch repair deficiency group

Tumors with the DNA mismatch repair (MMR) not functioning are phenotypically identified by the presence of microsatellite instability (MSI). The MMR is a pathway that recognizes and repairs incorrect insertion or deletion of bases during DNA replication. Mutations in the key genes *MLH1, MSH2, MSH6,* or *PMS2* can be germline or somatic, resulting in MMR deficiency (MMRd) tumors. About 30% of all ECs belong to this group and are distinguished by low copy-number aberrations and a high mutational burden. The *MLH1* promoter methylation is the most common alteration in sporadic ECs.

Conversely, Lynch syndrome, known as hereditary non-polyposis colorectal cancer (HNPCC), is the consequence of a germline mutation in MMR genes and is found in 10–15% of MMRd patients. Patients with Lynch Syndrome have a cumulative lifetime risk of EC of 40–60% [20–22], compared to 3,1% of the general population [23]. Family members relatives to Lynch syndrome patients must undergo genetic evaluations to detect MMR genes alterations and, if present, start an adequate oncological screening [24]. Overall, the prognosis for patients with this molecular profile is intermediate [19].

3.3 p53-abnormal group

The tumor suppressor gene *TP53*, which encodes for the p53 protein, is one of the most common mutations in human tumors [25]. Mutation in *TP53* gene is detached in 90% of tumors characterized by a high number of somatic copy-number alterations and a low mutational rate [8]. They include 8–24% of EC; most of them have a serous or mixed histology and present at higher stages with a high grade of differentiation. However, a small number of low-grade ECs in early stages harbor a p53 mutation. *TP53* mutation status is not equivalent to the copy-number high subgroup of patients in TCGA, but it identifies cases where the prognosis is usually unfavorable. In clinical setting, IHC for p53 is the preferred tool, being low-cost even if not completely correspondent to *TP53* mutation status [19,26].

3.4 p53 wild-type/no specific molecular profile group

The EC group that does not exhibit *POLE* mutations, mismatch repair or p53 abnormalities is classified as no specific molecular profile (NSMP) or p53 wild-type. Approx-

imately 50% of ECs exhibits this molecular profile. These tumors, predominantly of endometrioid histology, are characterized by microsatellite stability, a low mutational burden, and low copy-number aberrations, with a high estrogen and progesterone receptors expression. Overall, the prognosis for patients in this genomic class is intermediate [19].

3.5 Multiple-classifier group

A small number of ECs harbor more than one molecular classifying feature and are defined as "multiple classifiers". In these cases, when *POLE* and p53 are both mutated, the prognosis is established by *POLE*. In the same way, if MMR and p53 are both mutated, the prognosis is established by MMRd [27]. However, prognosis of multiple classifiers is still an evolving issue.

The recent ESGO/ESTRO/ESP guidelines, published at the end of 2020, incorporate these molecular features with the traditional clinicopathological factors to better guide the adjuvant treatment choice using an integrated classification system [2]. Risk groups consider both cases that undergo molecular assessment and cases that do not. EC patients are classified using the standard pathologic features, if molecular profiling is not known.

Clinicopathological factors are the traditional ones described in the ESMO/ESGO/ESTRO consensus in 2016 (see Table 1), with some clarifications:

- tumor differentiation grade defines grade 1 and grade 2 carcinomas as low-grade, and grade 3 carcinomas as high-grade;
- lymphovascular space involvement (LVSI) can be described as absent, focal if there is a single focus of LVSI around the tumor, substantial if there is a multifocal or diffuse arrangement of LVSI, or the presence of tumor cells in five or more lymphovascular spaces [2].

Molecular features include the categories resulted in the TCGA analysis [8]:

- *POLE*mut, analyzed by DNA sequencing;
- p53, assessed by immunohistochemistry;
- MLH1, MSH2, MSH6, and PMS2, assessed by immunohistochemistry;
- no specific molecular profile.

4. The 2020 ESGO/ESTRO/ESP risk classification for EC

4.1 Low-risk class

The Low-risk group includes patients with the following histopathological and/or molecular characteristics:

- stage IA endometrioid, low-grade, LVSI negative or focal;
- stage I–II *POLE*mut endometrial carcinoma, without residual disease;
- stage IA MMRd/NSMP endometrioid carcinoma, low-grade, LVSI negative or focal [2].

According to the new ESGO/ESTRO/ESP guidelines, adjuvant treatment is not recommended in this group of patients. Many randomized trials reported higher toxicity without any improvement in prognosis using radiotherapy (RT) as adjuvant treatment. Moreover, the number of recurrences after surgery alone is very low in this group, less than 5% in stage I [28].

Adjuvant treatment seems not to be justifiable in patients with stage I–II *POLE*mut EC.

In the molecular analysis of the PORTEC-3 trial of high-risk ECs, patients with *POLE*mut endometrioid carcinoma had an excellent outcome in both arms. However, both trial arms included adjuvant treatment with external beam radiation therapy (EBRT).

Currently, based on the scientific evidence, the omission of adjuvant treatment for patients with stage III–IVA, *POLE*mut EC is controversial because of limited data. Prospective studies are needed to understand the prognosis in these specific groups of patients [29].

4.2 Intermediate-risk class

The Intermediate-Risk group includes patients with the following histopathological and/or molecular characteristics:

- Stage IB endometrioid, low-grade, LVSI negative or focal;
- Stage IA endometrioid, high-grade, LVSI negative or focal;
- Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion;
- Stage IB MMRd/NSMP endometrioid carcinoma, low-grade, LVSI negative or focal;
- Stage IA MMRd/NSMP endometrioid carcinoma, high-grade, LVSI negative or focal;
- Stage IA p53-abnormal and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion [2].

Many randomized trials have shown that, in the observational arm, the site where loco-regional relapses occur most frequently after surgery, in intermediate-risk patients, is the vaginal vault. Adjuvant brachytherapy guarantees vaginal control and an excellent overall survival, similar to those obtained in patients treated with adjuvant EBRT [30–35]. Moreover, in a randomized study of patients in stage I of disease, survival was not affected by adding primary pelvic RT to brachytherapy. However, RT caused a reduction in loco-regional recurrences and a shift of the first recurrence from loco-regional to non-loco-regional metastasis.

A Danish population study confirmed that the risk of loco-regional relapse was higher (about 14%) in the observational arm without brachytherapy. However, overall survival was not different due to the effectiveness of the treatment of the relapse in patients who were not previously irradiated [36].

According to the long-term follow-up of Alders' trial, a significant reduction in vaginal and pelvic recurrences was found in the vaginal plus pelvic radiotherapy group (group B) compared with the vaginal radiotherapy alone group (group A). On the other hand, more patients in group B developed distant metastases than those in group A, with the 5-year survival rate not improved by external irradiation. This finding underlines the consequence of postoperative EBRT in low and intermediate-risk patients, suggesting increased toxicity and side effects especially in young patients [37].

Future treatments should be focused on avoiding metastatic disease that influences overall survival instead of preventing local relapse. In this view, vaginal brachytherapy is recommended as adjuvant treatment for patients with intermediate-risk EC, with less vaginal recurrences but no effect on survival rate. No adjuvant treatment can be considered in this group, especially for patients younger than 60 years who have a lower risk of relapse.

According to some case series, in stage I type 2 EC, vaginal brachytherapy might be successful in preventing vaginal relapse, while others underlined the improvement in the patient's overall survival after adjuvant chemotherapy. Based on these contradictory results, the experts suggest discussing the management of these patients individually, because the evidence is not sufficient to support a single recommendation.

There are no randomized trials available and very little data on the best treatment for stage IA non-endometrioid and/or p53-abnormal carcinomas without myometrial invasion. Adjuvant treatment should be discussed case by case. However, new standards suggest no treatment for p53-abnormal EC restricted to a polyp or without myometrial invasion [2].

4.3 High-intermediate-risk class

The High-Intermediate-Risk group includes patients with the following histopathological and/or molecular characteristics:

- Stage I endometrioid, substantial LVSI regardless of grade and depth of invasion;

- Stage IB endometrioid high-grade regardless of LVSI status;

- Stage II;

- Stage I MMRd/NSMP endometrioid carcinoma, substantial LVSI regardless of grade and depth of invasion;

- Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVSI status;

- Stage II MMRd/NSMP endometrioid carcinoma [2].

The decision for adjuvant treatment in this risk group is different whether lymph-nodal status is known and negative, because lymphadenectomy or sentinel lymph node dissection has been performed, or the lymph-nodal status is not known because lymph-node staging was not performed.

4.3.1 pN0 after lymph node staging

If the lymph-nodal status is negative after surgical staging (lymphadenectomy or sentinel lymph node dissection), the new guidelines recommend adjuvant brachytherapy to reduce vaginal recurrence. In the case of substantial LVSI and/or stage II, EBRT can be indicated as it has been shown to reduce the risk of pelvic and para-aortic lymph-node disease [38].

According to the result of two randomized trials on high-intermediate risk patients, there was no difference between adjuvant chemotherapy alone and EBRT alone in recurrence-free and overall survival. However, both the trials reported that radiation treatment reduced loco-regional recurrences, while chemotherapy was associated with a better systemic disease control [39,40].

The association of chemotherapy and radiotherapy seemed to produce better recurrence-free and overall survival outcomes than radiotherapy alone in the NSGO/EORTC and the PORTEC-3 trials [40,41].

In the GOG-249 trial there was no improvement in recurrence-free or overall survival from three cycles of chemotherapy with brachytherapy compared with EBRT alone [38].

The molecular analysis performed in the PORTEC-3 trial showed that chemotherapy gives no benefit for MMRd carcinomas [29,42]. According to these results, in early stage of disease, the omission of adjuvant treatment is an option if supported by a close follow-up.

4.3.2 pNx (lymph node staging not performed)

When the lymph-nodal status is unknown, based on the randomized trials GOG-249 (for stage I–II ECs with high-risk factors or serous or clear cell histology), the PORTEC-3 trial and the GOG-99 trial, adjuvant EBRT is recommended in the presence of substantial LVSI or stage II disease [38,41–43]. The PORTEC-3 trial suggests the benefit of the addition of adjuvant chemotherapy, especially for high-grade carcinomas. Chemotherapy can be an option for ECs characterized by a high-grade tumor or a substantial LSVI. Adjuvant brachytherapy alone is also an option for LVSI negative cases and stage II low-grade disease.

Multi-disciplinary decision-making is important to choose the better therapy with less toxicity for stage I–II endometrioid carcinoma [42].

Molecular analysis of PORTEC-3 trial did not show any benefit of chemotherapy for MMRd carcinomas [29].

4.4 High-risk class

The high-risk group includes patients with the following histopathological and/or molecular characteristics:

- stage III–IVA with no residual disease;

- stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease;

- stage III–IVA MMRd/NSMP endometrioid carcinoma with no residual disease;
- stage I–IVA p53-abnormal endometrial carcinoma with myometrial invasion, with no residual disease;
- stage I–IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease [2].

The PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and concurrent chemo-radiotherapy (two cycles of cisplatin during radiotherapy followed by four cycles of carboplatin-paclitaxel) versus pelvic radiotherapy alone for women with high-risk endometrial cancer. In 2019, after five years of follow-up, the updated results were published. The trial showed a significant overall survival benefit at five years and a failure-free survival benefit in the combined therapy group compared with radiotherapy alone [44]. The most significant overall survival difference was seen in stage III carcinomas and in serous carcinomas regardless of stage. In stage I–II patients, the addition of chemotherapy to radiotherapy should be discussed after evaluating risks and benefits.

The GOG-258 study was a randomized phase III trial evaluating six cycles of chemotherapy alone (consisting of carboplatin plus paclitaxel) versus radiation therapy followed by four cycles of chemotherapy in patients with stage III–IVA endometrial cancer. Eventually, the combined regimen was not superior to chemotherapy alone in prolonging relapse-free survival. However, vaginal or pelvic and paraaortic lymph-node recurrences were less frequent in the combined regimen arm, while distant recurrence was more common in the chemo-radiotherapy group [45].

The molecular sub-group analysis of the PORTEC-3 trial reported a statistically significant survival benefit for p53-abnormal carcinomas with combined therapy in patients with stage I–III p53-abnormal ECs with myometrial infiltration; even stage III NSMP ECs showed some advantage from the addition of chemotherapy. This effect was not clear for MMRd carcinomas. Currently, there is still limited data for stage III–IVA POLEmut EC and stage I–IVA MMRd/NSMP clear cell EC to allocate them into a prognostic risk group.

In conclusion, the recommendations for this high-risk group of patients consist of EBRT with concurrent and adjuvant chemotherapy or, the alternative, sequential chemotherapy and radiotherapy. Chemotherapy alone can also be considered as an option [2].

5. Ongoing trials

The recent evidence and the 2020 ESGO/ESTRO/ESP recommendations for EC underline the need to consider new molecular prognostic features to more effectively choose the adjuvant treatment, historically based only on clinicopathological risk factors.

The PORTEC-4a trial is a prospective, multicenter, randomized phase III ongoing trial conducted to compare the individualized choice of adjuvant treatment, based on a molecular-integrated risk profile, to standard adjuvant vaginal brachytherapy in women with high-intermediate risk ECs. Patients are divided into three sub-groups: favorable, intermediate and unfavorable (Fig. 1). In the experimental arm, patients belonging to the favorable group will not receive any adjuvant treatment. Conversely, they will receive standard adjuvant vaginal brachytherapy or pelvic radiotherapy according to their indeterminate or unfavorable profile, respectively (Fig. 2). The hypothesis of this study is that adjuvant treatment based on a molecular-integrated risk profile is similar to standard adjuvant brachytherapy in preventing recurrences in this group of patients. In some cases, patients would not receive any adjuvant treatment leading to less morbidity and a benefit in healthcare costs [46].
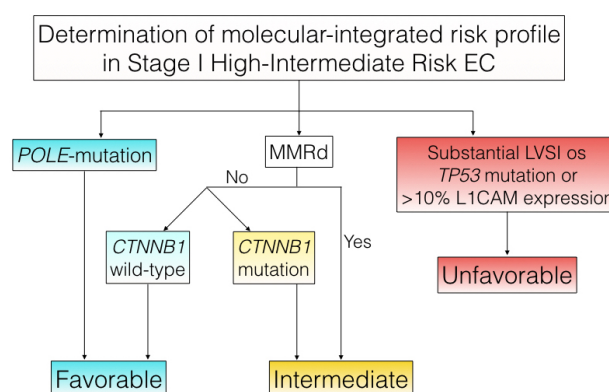

Fig. 1. Molecular-integrated risk profile in the PORTEC-4a trial.

Additional molecular features are included and evaluated in the PORTEC-4a trial: *CTNNB1* mutation and L1CAM expression.

CTNNB1 is a gene encoding b-catenin protein, that regulates and coordinates cell adhesion and gene transcription. Studies showed that EC patients bearing *CTNNB1* gene mutation have poorer disease-free and overall survival, especially within the copy number low group. Conversely, *CTNNB1*-wild type tumors showed better prognosis [6].

L1CAM is a transmembrane glycoprotein implicated in neurogenesis. This protein is frequently localized in tumor cells close to the stroma, suggesting its role in migration and invasion. Studies demonstrated that L1CAM-positive EC patients have an actual increased risk for distal or local recurrences [47,48].

In the era of personalized medicine, targeted agents in the adjuvant setting are under investigation.

A phase II trial showed an improvement in progression-free survival and overall survival, adding the HER2-targeted agent trastuzumab to the standard chemotherapy regimen in the adjuvant setting in patients
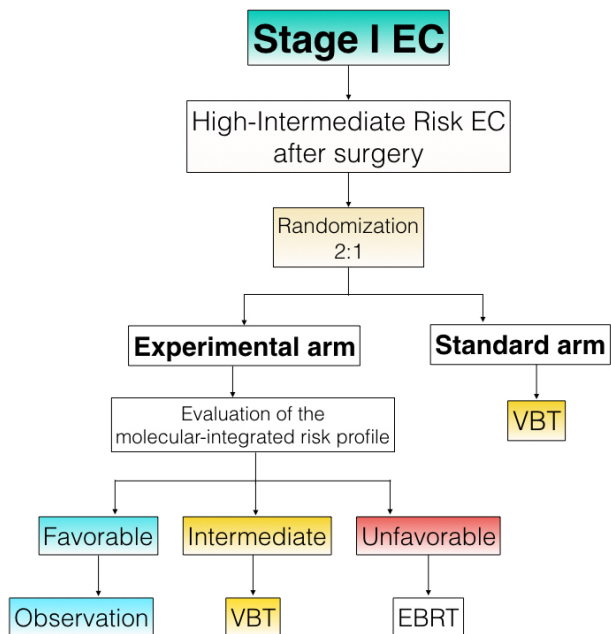
Fig. 2. Trial design of the PORTEC-4a trial.

with advanced serous EC (stage III–IV) [49].

*POLE*mut and MMRd ECs are hypermutated tumors characterized by a high mutational burden and high immunogenicity. The high level of neoantigens in these tumors activates the immune system, attracting tumor-infiltrating lymphocytes. However, the interaction between programmed death-ligand 1 (PD-L1) receptor expressed on cancer cells and programmed death protein 1 (PD-1) on activated T cells leads to the inhibition of the immunological response [50,51]. Hence, the effect of checkpoint inhibitors has been studied in several trials in advanced or metastatic solid tumors with MMRd, and promising results have also been seen in the EC population [52,53]. In April 2021, the Food and Drug Administration (FDA) approved an anti-PD-1 monoclonal antibody, Dostarlimab, for patients with recurrent or metastatic MMRd EC with at least one prior line of platinum-based chemotherapy [54]. However, the role of immunotherapy in the adjuvant setting is still being studied.

In one ongoing randomized clinical trial (ClinicalTrials.gov Identifier: NCT04214067), Pembrolizumab, an anti-PD-1 monoclonal antibody, will be added to standard radiation therapy in patients with high–intermediate risk MMRd Ecs in stages I–II [55].

Homologous recombination deficiency has been observed frequently in the p53-abnormal subclass of EC. No data are yet available on the effect of PARP inhibition in patients with EC. However, combination treatment targeting homologous recombination deficiency using platinum-based chemotherapy with PARP inhibitors seems promising, based on the similarities with high-grade ovarian cancer that harbors the same *TP53* mutational profile [51,56].

The RAINBO program is an international, multicenter study composed of three randomized trials and one observational trial, planned to compare different adjuvant treatments in patients with high-risk and advanced-stage EC, according to their molecular profile. P53-abnormal EC patients will receive a maintenance therapy with Niraparib, a PARP inhibitor, after a combined chemo-radiation treatment. The role of anti-PD-L1 inhibitors after EBRT will be studied in MMRd ECs with substantial LVSI. In EC patients characterized by a NSMP, hormone adjuvant therapy will be added to EBRT instead of chemotherapy. *POLE*mut EC patients will not receive any adjuvant therapy and will be part of the observational trial (Fig. 3).
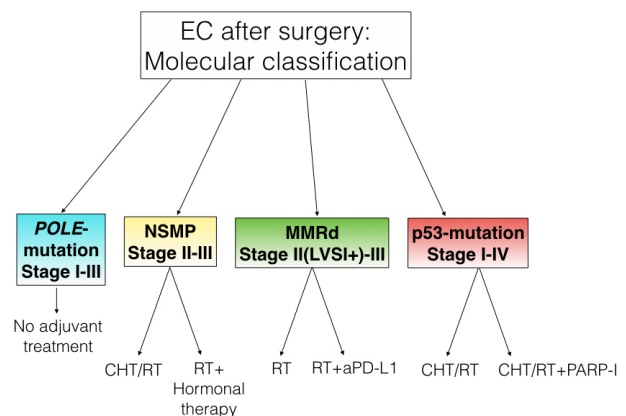

Fig. 3. Trial design of the RAINBO trial.

6. Conclusions

The ESGO-ESTRO-ESP guidelines updated at the end of 2020 are the first step forward to improve the classification and the management of endometrial cancer patients for a more appropriate and individualized medicine. Moreover, new perspectives for the adjuvant therapy of EC are being evaluated in ongoing studies.

The dualistic terminology to define EC as type 1 and type 2 should be dropped in this new era of precision medicine; molecular profiling must be encouraged in all ECs, especially in high-grade tumors. *POLE*-mutation analysis may be omitted in low-risk and intermediate-risk EC with low-grade histology. Its application to low-grade endometrioid carcinomas may not be cost-effective.

However, at present, the new molecular classification is not routinely performed in all centers where ECs are diagnosed. If IHC for MMR and p53 are easily accessible, *POLE* sequencing is not widely available in all laboratories, or it takes weeks to get the result. In the absence of a complete molecular profiling, clinicopathological features remain the only tool to take into consideration to decide when and which type of adjuvant therapy is better to offer to patients. Research needs to work on this crucial point.

In conclusion, the RAINBO and PORTEC-4a prospective trials will help to understand the actual role of a molecular-based classification on patients' prognosis and potentially change the way we approach this disease. Until then, adjuvant treatment decisions must be taken in a multidisciplinary setting, especially in those cases where the current evidence is insufficient to support a single recommendation.

Author contributions

MP and AAL designed the review. TG, MA and BZ helped in the analysis and interpretation of the literature. GDM, LB and FL provided advice on drafting the article. All authors contributed to write the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Mar-nitz S, *et al*. ESGO/ESTRO/ESP Guidelines for the Management of Patients with Endometrial Carcinoma. International Journal of Gynecological Cancer. 2021; 31: 12–39.

[3] Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecologic Oncology. 1983; 15: 10–17.

[4] Creutzberg CL, van Putten WLJ, Koper PC, Lybeert MLM, Job-sen JJ, Wárlám-Rodenhuis CC, *et al*. Survival after relapse in patients with endometrial cancer: results from a randomized trial.Gynecologic Oncology. 2003; 89: 201–209.

[5] Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecologic Oncology. 2006; 101: 520–529.

[6] Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, *et al*. ESMO–ESGO–ESTRO consensus con-ference on endometrial cancer: Diagnosis, treatment and follow-up. Radiotherapy and Oncology. 2016; 117: 559–581.

[7] Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, *et al*. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer—Combined Analysis of the PORTEC Cohorts. Clinical Cancer Research. 2016; 22: 4215–4224.

[8] Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497: 67–73.

[9] Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, *et al*. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017; 123: 802–813.

[10] Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, *et al*. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Annals of Oncology. 2018; 29: 1180–1188.

[11] Plotkin A, Kuzeljevic B, De Villa V, Thompson EF, Gilks CB, Clarke BA, *et al*. Interlaboratory Concordance of ProMisE Molecular Classification of Endometrial Carcinoma Based on Endometrial Biopsy Specimens. International Journal of Gynecological Pathology. 2020; 39: 537–545.

[12] Alexa M, Hasenburg A, Battista MJ. The TCGA Molecular Classification of Endometrial Cancer and Its Possible Impact on Adjuvant Treatment Decisions. Cancers. 2021; 13: 1478.

[13] León-Castillo A, Britton H, McConechy MK, McAlpine JN, Nout R, Kommoss S, *et al*. Interpretation of somatic POLE mutations in endometrial carcinoma. The Journal of Pathology. 2020; 250: 323–335.

[14] Piulats JM, Guerra E, Gil-Martín M, Roman-Canal B, Gatius S, Sanz-Pamplona R, *et al*. Molecular approaches for classifying endometrial carcinoma. Gynecologic Oncology. 2017; 145: 200–207.

[15] Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, *et al*. Prognostic Significance of POLE Proofreading Mutations in Endometrial Cancer. JNCI: Journal of the National Cancer Institute. 2014; 107: 402.

[16] McConechy MK, Talhouk A, Leung S, Chiu D, Yang W, Senz J, *et al*. Endometrial Carcinomas with POLE Exonuclease Domain Mutations have a Favorable Prognosis. Clinical Cancer Research. 2016; 22: 2865–2873.

[17] Church DN, Briggs SE, Palles C, Domingo E, Kearsey SJ, Grimes JM, *et al*. DNA polymerase epsilon and delta exonuclease domain mutations in endometrial cancer. Human Molecular Genetics. 2013; 22: 2820–2828.

[18] Meng B, Hoang LN, McIntyre JB, Duggan MA, Nelson GS, Lee C, *et al*. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. Gynecologic Oncology. 2014; 134: 15–19.

[19] Raffone A, Travaglino A, Mascolo M, Carbone L, Guida M, Insabato L, *et al*. TCGA molecular groups of endometrial cancer: Pooled data about prognosis. Gynecologic Oncology. 2019; 155: 374–383.

[20] Meyer LA, Broaddus RR, Lu KH. Endometrial Cancer and Lynch Syndrome: Clinical and Pathologic Considerations. Cancer Control. 2009; 16: 14–22.

[21] Dunlop M. Cancer risk associated with germline DNA mismatch repair gene mutations. Human Molecular Genetics. 1997; 6: 105–110.

[22] Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, *et al*. Cancer risk in mutation carriers of DNA-mismatch-repair genes. International Journal of Cancer. 1999; 81: 214–218.

[23] SEER Training Modules, Cancer Stat Facts: Uterine Cancer. U. S. National Institutes of Health, National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/corp.html (Accessed: 13 December 2021).

[24] Mills AM, Liou S, Ford JM, Berek JS, Pai RK, Longacre TA. Lynch Syndrome Screening should be Considered for all Patients with Newly Diagnosed Endometrial Cancer. American Journal of Surgical Pathology. 2014; 38: 1501–1509.

[25] Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, *et al*. Mutational landscape and significance across 12 major cancer types. Nature. 2013; 502: 333–339.

[26] Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, *et al*. A clinically applicable molecular-based classification for endometrial cancers. British Journal of Cancer. 2015; 113: 299–310.

[27] León-Castillo A, Gilvazquez E, Nout R, Smit VT, McAlpine JN, McConechy M, *et al*. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. The Journal of Pathology. 2020; 250: 312–322.

[28] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, *et al*. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. The Lancet. 2000; 355: 1404–1411.

[29] León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, *et al*. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit from Adjuvant Therapy. Journal of Clinical Oncology. 2020; 38: 3388–3397.

[30] Nout R, Smit V, Putter H, Jürgenliemk-Schulz I, Jobsen J, Lutgens L, *et al*. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. The Lancet. 2010; 375: 816–823.

[31] Barney BM, Petersen IA, Mariani A, Dowdy SC, Bakkum-Gamez JN, Haddock MG. The Role of Vaginal Brachytherapy in the Treatment of Surgical Stage i Papillary Serous or Clear Cell Endometrial Cancer. International Journal of Radiation Oncology, Biology, Physics. 2013; 85: 109–115.

[32] R.A. S, Bhavsar D, M.N. S, Kunikullaya US, R.K. V, Parikh A, *et al*. Combined external beam radiotherapy and vaginal brachytherapy versus vaginal brachytherapy in stage i, intermediate- and high-risk cases of endometrium carcinoma. Journal of Contemporary Brachytherapy. 2018; 10: 105–114.

[33] Cham S, Huang Y, Tergas AI, Hou JY, Burke WM, Deutsch I, *et al*. Utility of radiation therapy for early-stage uterine papillary serous carcinoma. Gynecologic Oncology. 2017; 145: 269–276.

[34] Shinde A, Li R, Amini A, Chen Y, Cristea M, Dellinger T, *et al*. Improved survival with adjuvant brachytherapy in stage IA endometrial cancer of unfavorable histology. Gynecologic Oncology. 2018; 151: 82–90.

[35] Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External Pelvic and Vaginal Irradiation Versus Vaginal Irradiation alone as Postoperative Therapy in Medium-Risk Endometrial Carcinoma—a Prospective Randomized Study. International Journal of Radiation Oncology, Biology, Physics. 2012; 82: 1249–1255.

[36] Ørtoft G, Hansen ES, Bertelsen K. Omitting Adjuvant Radiotherapy in Endometrial Cancer Increases the Rate of Locoregional Recurrences but has no Effect on Long-Term Survival. International Journal of Gynecological Cancer. 2012; 23: 1429–1437.

[37] Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative External Irradiation and Prognostic Parameters in Stage I Endometrial Carcinoma: Clinical and histopathologic Study of 540 Patients. Obstetrics & Gynecology. 1980; 56: 419–427.

[38] Randall ME, Filiaci V, McMeekin DS, von Gruenigen V, Huang H, Yashar CM, *et al*. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early-Stage Endometrial Cancer. Journal of Clinical Oncology. 2019; 37: 1810–1818.

[39] Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, *et al*. Adjuvant chemotherapy vs radiotherapy in high-risk en-

dometrial carcinoma: results of a randomised trial. British Journal of Cancer. 2006; 95: 266–271.

[40] Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, *et al*. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecologic Oncology. 2008; 108: 226–233.

[41] Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, *et al*. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer–Results from two randomised studies. European Journal of Cancer. 2010; 46: 2422–2431.

[42] de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, *et al*. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. The Lancet Oncology. 2018; 19: 295–309.

[43] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, *et al*. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecologic Oncology. 2004; 92: 744–751.

[44] de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, *et al*. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. The Lancet Oncology. 2019; 20: 1273–1285.

[45] Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, *et al*. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. New England Journal of Medicine. 2019; 380: 2317–2326.

[46] van den Heerik ASVM, Horeweg N, Nout RA, Lutgens LCHW, van der Steen-Banasik EM, Westerveld GH, *et al*. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. International Journal of Gynecologic Cancer. 2020; 30: 2002–2007.

[47] Zeimet AG, Reimer D, Huszar M, Winterhoff B, Puistola U, Abdel Azim S, *et al*. L1CAM in Early-Stage Type i Endometrial Cancer: Results of a Large Multicenter Evaluation. JNCI: Journal of the National Cancer Institute. 2013; 105: 1142–1150.

[48] Corrado G, Laquintana V, Loria R, Carosi M, de Salvo L, Sperduti I, *et al*. Endometrial cancer prognosis correlates with the expression of L1CAM and miR34a biomarkers. Journal of Experimental & Clinical Cancer Research. 2018; 37: 139.

[49] Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, *et al*. Randomized Phase II Trial of Carboplatin–Paclitaxel Compared with Carboplatin–Paclitaxel–Trastuzumab in Advanced (Stage III–IV) or Recurrent Uterine Serous Carcinomas that Overexpress her2/Neu (NCT01367002): Updated Overall Survival Analysis. Clinical Cancer Research. 2020; 26: 3928–3935.

[50] Keir M, Francisco L, Sharpe A. PD-1 and its ligands in T-cell immunity. Current Opinion in Immunology. 2007; 19: 309–314.

[51] Post CCB, Westermann AM, Bosse T, Creutzberg CL, Kroep JR. PARP and PD-1/PD-L1 checkpoint inhibition in recurrent or metastatic endometrial cancer. Critical Reviews in Oncology/Hematology. 2020; 152: 102973.

[52] Lee V, Murphy A, Le DT, Diaz LA. Mismatch Repair Deficiency and Response to Immune Checkpoint Blockade. The Oncologist. 2016; 21: 1200–1211.

[53] Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord J, *et al*. Efficacy of Pembrolizumab in Patients with Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results from the Phase

II KEYNOTE-158 Study. Journal of Clinical Oncology. 2020; 38: 1–10.

[54] Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, *et al*. Clinical Activity and Safety of the Anti–Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients with Recurrent or Advanced Mismatch Repair–Deficient Endometrial Cancer. JAMA Oncology. 2020; 6: 1766.

[55] US National Library of Medicine. Testing the addition of the immunotherapy drug, pembrolizumab, to the usual radiation treatment for newly diagnosed early stage high intermediate risk endometrial cancer. 2021. Available at: https://clinicaltrals.gov/ct2/show/NCT04214067 (Accessed: 18 November 2021).

[56] de Jonge MM, Auguste A, van Wijk LM, Schouten PC, Meijers M, ter Haar NT, *et al*. Frequent Homologous Recombination Deficiency in High-grade Endometrial Carcinomas. Clinical Cancer Research. 2019; 25: 1087–1097.