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Review

High risk endometrial cancer: Clues towards a revision of the therapeutic paradigm

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ABSTRACT

Introduction: Endometrial cancer (EC) is a major cause of mortality worldwide with nearly 200 000 cases diagnosed annually. The recent ESMO-ESGO-ESTRO guidelines include a new classification defining a heterogeneous high-risk group of recurrence (HR) comprising: (i) endometrioid (type 1) FIGO stage IB grade 3 tumors (type 1/G3ECs), (ii) non-endometrioid tumors (type 2) and (iii) advanced stages whatever the histological type (Colombo et al., 2016).
Areas covered: The aim of this review is to summarize current evidence for therapeutic approaches in HR-EC according to the updated ESMO-ESGO-ESTRO classification by discussing the following issues: i) HR-EC heterogeneity, (ii) prognostic factors and current classification, and (iii) optimal staging strategies (site and extent) and the role of adjuvant treatment.
Expert commentary: HR-EC treatment is based on surgery, radiation therapy, brachytherapy, and chemotherapy, either alone or sequentially, in combination with other treatments depending on disease stage, histological grade and risk group. Specific trials are needed to establish the role of systematic pelvic and paraaortic lymphadenectomy, adjuvant therapies and targeted drugs. Although molecular characterization has been reported to customize therapeutic strategies and thereby improve therapeutic outcomes in EC, none of the targeted agents investigated (antiangiogenic and mTOR/PI3K pathway inhibitor agents) have resulted in a change in clinical practice in HR-EC.

Contents

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1. Introduction

Endometrial cancer (EC) is a major cause of mortality worldwide with nearly 200 000 cases diagnosed every year. Although its incidence differs throughout the world, it is estimated to be the most common cancer of the female genital tract and the fourth most common cancer in North America and Europe [1,2]. Age-adjusted annual incidence was 24.3 per 100 000 women in the USA in 2006–10, and 19.4 per 100 000 in the UK in 2008 [3–5].

About three-quarters of women with EC are diagnosed at an early stage (International Federation of Gynecology and Obstetrics (FIGO) stages I or II), for which prognosis is good with a 5-year overall survival (OS) ranging from 74 to 91% [2,6,7]. However, the recently updated ESMO-ESGO-ESTRO guidelines address a new classification which defines a heterogeneous high-risk (HR) group of recurrence including: (i) endometrioid (type 1) FIGO stage IB grade 3 tumors (type 1/G3ECs), (ii) non-endometrioid tumors (type 2) and (iii) advanced stages whatever the histological type [1]. This HR group has a poorer prognosis with an increased risk of metastatic disease and recurrence [1,8–10]. Although the OS rates differ widely from one study to another, it is estimated that the 5-year OS varies from 57% to 66% for FIGO stages III and from 20% to 26% for FIGO stages IV [6]. Similarly, recurrence rates vary from 33% to 79%, respectively [8,9,11,12].

In the past decade, the therapeutic paradigm of HR-EC has changed substantially [13–16]. Despite the publication of national and international guidelines, the therapeutic approach often boils down to the individual physician's preferences [1,4,17–19]. When analyzing published data, considerable heterogeneity needs to be taken into account including: (i) the absence of a consensual classification to define HR-EC; (ii) the low number of studies and their retrospective nature; and (iii) the lack of randomized controlled studies focusing specifically on HR-EC patients. This lack of unequivocal evidence is responsible for wide variations in surgical and adjuvant management of HR-EC [10,13,19–23].

Hence, the aim of this review was to summarize the available evidence about therapeutic approaches for HR-EC patients according to the ESMO-ESGO-ESTRO classification [1] discussing following issues: i) HR-EC heterogeneity; (ii) prognostic factors and current classification of HR-EC; and (iii) optimal lymph node (LN) staging strategy (site and extent) and the role of adjuvant treatment.

A systematic literature search of the MEDLINE/Pubmed and Scopus database was performed using the following keywords in combination with both Medical Subject Heading terms and text words: endometrial cancer, high-risk, nodal status, surgical techniques, lymphadenectomy, adjuvant therapies. Only English-language original and review articles published from January 2010 to September 2017 were included. The relevant studies selected were analyzed and summarized after an interactive peer-review process of the panel.

2. A clinically and genetically heterogeneous HR disease

Traditionally, EC have been classified as type I or type II, as defined by Bokhman, on the basis of clinical, endocrine, and epidemiological observations. Type I tumors are estrogen dependent and associated with endometrial hyperplasia, whereas type II tumors are estrogen independent and associated with endometrial atrophy [24]. EC is also classified according to histopathological characteristics with the most common subtypes being endometrioid carcinoma, serous carcinoma, carcino-sarcoma, and clear-cell carcinoma [25]. It has been demonstrated that EC comprises a biologically, clinically, morphologically, and genetically heterogeneous behavior especially for the HR group of patients [14,16,26,27].

A number of authors have recently identified common molecular alterations in several important genes in EC [16,26,28–30]. In this specific setting, the Cancer Genome Atlas Research Network, based on a comprehensive molecular profiling of 373 ECs, suggested that the traditional dualistic model could be improved by a classification compromising four molecular subgroups with a potential prognostic significance: (i) DNA polymerase epsilon (POLE) ultramutated; (ii) microsatellite instability hypermutated; (iii) copy-number low; and (iv) copy-number high (serous-like and mostly TP53 mutant) [16]. Based on data from the TransPORTEC group, an international consortium related to the PORTEC3 trial, Stelloo et al. [28] investigated whether these molecular subgroups could be used to refine risk assessment in HR-EC. They identified four prognostic subgroups in a population of 116 HR-EC patients [1]: a group with p53-mutant tumors [2]; a group with microsatellite unstable tumors [3]; a group with POLE proofreading-mutant tumors; and [4] a group with no specific molecular profile (NSMP). In the POLE-mutant (n = 14) and microsatellite unstable (n = 19) patients, no distant metastasis occurred, compared with a 50% rate of distant metastasis in the p53-mutant (n = 36) and 39% in the NSMP groups ($P < 0.001$). 5-year recurrence-free survival was 93% and 95% for POLE-mutant and microsatellite unstable groups, 42% for the p53-mutant group and 52% for the NSMP group ($P < 0.001$). These results suggest that POLE-mutant and microsatellite unstable HR patients have a favorable prognosis and that the current risk assessment of these patients may therefore be overestimated, possibly resulting in overtreatment. In contrast, group 1 tumors that have a p53-mutant like expression and group 4 tumors with no specific molecular profile are true HR cancers. These results may provide a rationale to investigate not only the use of PI3K-AKT pathway inhibitors in this selected patient group but also hormonal treatment in those tumors with retained receptor expression remaining an option.

In this context, the PORTEC-4A trial (NTR5841) was developed to select patients with early-stage EC based on their molecular profile for adjuvant radiation (Netherlands Trials Registry: NTR5841).

3. Available prognostic factors and current classification of HR-EC

Understanding key factors is critical when making decisions about an appropriate therapeutic approach (surgical management and indications for adjuvant therapies). HR factors are (combinations of) advanced age, high-grade, non-endometrioid histology, extensive lymphovascular space invasion (LVSI), and more advanced disease stage [1,8,13,24,27,31–33]. These factors have been combined to define HR-EC and are currently used worldwide to guide decision making and clinical trial design [1,9,18,19,22] (Table 1). However, there is some debate as to whether type 1/G3ECs should be classified as HR-EC along with type 2 ECs. Several authors justify the inclusion of type 1/G3ECs in the HR group due to the frequency of their coexistence and similarities in clinical characteristics and molecular aspects with G3EC and type 2 cancers. While the recent ESMO-ESGO-ESTRO guidelines validate the incorporation of type 1/G3ECs as HR-EC [1], other major classifications [14,18,19,22] used to design clinical trials and adjuvant therapy management exclude type 1/G3EC located in the corpus uteri from the HR group. In addition, it is unclear whether HR patients should be considered as an additional subgroup of patients defined initially in the PORTEC-1 [19] and GOG99 [22] studies as high-intermediate risk (HIR) group by the combination of poor prognostic criteria, i.e., (i) occurring at any age with three of the risk factors mentioned above, (ii) in women $\geq$ 50 years with two risk factors, and (ii) in women $\geq$ 70 years

Table 1
Description of HIR and HR EC patients according to six classification systems.

Classification and year of publication	Number of patients	Criteria to define HIR EC	Criteria to define HR EC
PORTEC-1 [19] **2000**	715	- Age >60 years with endometrioid type grade 1 or 2 histology and myometrial invasion >50% - Age >60 years with endometrioid type grade 3 histology and myometrial invasion <50%	- Stage III–IV disease - Uterine serous carcinoma or clear-cell carcinoma of any stage
GOG-99 [22] **2004**	382	- Age 50–69 years and ≤1 pathological risk factors*. Age ≥70 years and no pathological risk factors* - Any age and 3 pathological risk factors. Age 50–69 years and ≥2 pathological risk factors - Age ≥70 years and ≥1 pathological risk factors*	- Stage III–IV disease, irrespective of histology or grade - Uterine serous carcinoma or clear-cell carcinoma of any stage
SEPAL [18] **2010**	671	–	- Stage III or IV, any grade, any LVSI
ESMO-ESGO-ESTRO [1] **2015**	–	- Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSIstatus - Stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depthof invasion	- Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSIstatus - Stage II - Stage III endometrioid, no residual disease - - Non-endometrioid (serous or clear-cell or undifferentiated carcinoma, or carcinosarcoma)
ESMO modified [9] **2015**	496	- Stage IA grade 3 endometrioid type with LVSI. - Stage IB grade 1 and grade 2 endometrioid type with LVSI - Stage IB grade 3 endometrioid type with no LVSI	- Stage IB grade 3 endometrioid type with positive LVSI - Non-endometrioid disease of all stages

with at least one risk factor. The updated ESMO-ESGO-ESTRO guidelines suggest another combination including the LVSI criteria [1,9,27,34] (Table 1). In clinical practice, the impact of surgical staging and adjuvant therapies in women with (HIR) factors specifically has not been fully investigated [1]. Instead, these patients have been "lumped together" as women with HR disease, potentially obscuring any differences. Recently, Ouldamer et al. [35] investigated the rate of metastatic nodal disease in this specific ESMO/ESGO/ESTRO HIR group in a French multicenter study assessing the clinical impact of lymphadenectomy. The authors concluded that nodal staging should be systematically part of surgical staging for women with apparent HIR-EC. Evidence-based adjuvant treatment strategies have been proposed by the ESMO ESGO ESTRO guidelines for the HIR subgroup separating women who underwent LN staging from those who did not. However, no proposal has been forthcoming concerning optimal surgical staging, and especially the place of lymphadenectomy, probably because of a lack of data. Therefore, The ESMO/ESGO/ESTRO recommends either adjuvant vaginal brachytherapy in women with a negative LN status to decrease vaginal recurrence, or no adjuvant therapy.

3.1. Therapeutic approaches and challenges

3.1.1. Generality

EC treatment has become more complex over the past 5–10 years for several reasons: (i) changes in, and discrepancies between, the various classifications used to characterize recurrence risk factors that affect surgical management, adjuvant therapies, and prognosis [1,4,16,18]; (ii) changes in indications and modalities for lymphadenectomy (sentinel LN mapping (SLNM), pelvic +/- paraaortic LN dissection) [20,36–38]; (iii) changes in adjuvant therapy based on data from randomized trials [19,22]; and (iv) the emergence of studies on targeted therapies [14,16,26,29,39]. These modifications have led national scientific societies to review the emerging data and unanswered questions, and to publish specific recommendations for EC with specific therapeutic strategies for women with HR-EC (Tables 2 and 3).

In addition, it should be underlined here that many women with EC are of an advanced age and have comorbidities such as diabetes and obesity [40,41], which are important to bear in mind when considering the optimal treatment strategy. Indeed, morbid obesity poses challenges to surgery and the delivery of radiation and chemotherapy, conferring increased perioperative morbidity, a higher risk of radiation-related toxicity and the potential underdosing of chemotherapy [42–44].

3.1.2. Lymph node staging

In this chapter, we summarize current state of the art in LN assessment strategies to determine the current methods and indications for surgical LN staging (Table 2).

Guidelines about LN staging strategies in HR-EC are unclear and discordant. Controversy exists over indications and the therapeutic value of lymphadenectomy given the high heterogeneity of women in the HR-EC group and the low number of specific HR cases reported in the literature [20,36,45]. In addition, several questions have not been clearly answered by previous studies, such as: (i) the impact of LN staging on the oncological outcome and prognosis of HR-EC, (ii) optimal LN staging, and (iii) patient selection to determine the subgroup of HR women who may benefit the most from LN staging. Hence, indications for LN staging strategies differ substantially between authors and countries leading to widely differing practice patterns (Table 2).

The discrepancy between the various strategies that affect surgical management are in part explained by the results of two large randomized trials and a meta-analysis which failed to establish the therapeutic value of a systematic lymphadenectomy in stage I EC [20,36,45]. However, in the setting of HR-EC, these studies appear to be flawed by several design limitations rendering any conclusions at a low level of evidence. In practice, LN metastasis is a real indicator of poor prognosis which requires an adapted adjuvant therapy [35,46]. To date, lymphadenectomy is still the standard technique to assess the lymphatic spread of EC which leads many authors to support that identifying metastatic disease is crucial in women at HR to accurately select candidates for adjuvant treatment [11,47–52].

Table 2
Lymph node staging strategies for high risk endometrial cancer.

Guidelines Year of publication	HR definition	Recommendation
ESMO-ESGO-ESTRO [1] **2015**	• Grade 3 with deep myometrial invasion 950%) • In previously incompletely operated high-risk patients • Clinical or intra-operative stage II endometrial cancer • Non-EEC (apparent stage I)	• Lymphadenectomy should be recommended • Level of evidence: IV Strength of recommendation: B • Lymphadenectomy should be recommended • Level of evidence: V Strength of recommendation: C • Lymphadenectomy should be recommended • Level of evidence: IV Strength of recommendation: B • Lymphadenectomy should be recommended • Level of evidence: IV Strength of recommendation: B
National Comprehensive Cancer Network® (NCCN®) [4] **2016**	• High-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma features.	• Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging • SLN mapping can be considered (category 3) for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.
The British Gynaecological Cancer Society (BGCS) guidelines [69] **2017**	• High grade disease and non-endometrioid endometrial cancers	• Surgical staging, including pelvic and para-aortic lymphadenectomy
Society of Obstetricians and Gynecologists of Canada [70] **2013**	• High-risk disease (grade 2 or 3 adenocarcinoma / clear cell / papillary serous on biopsy)	• Pelvic and/or para-aortic lymphadenectomy • Level of evidence: II Strength of recommendation: 2B
Japan Society of Gynecologic Oncology guidelines [71] **2013**	• Endometrioid adenocarcinoma G3 and ≥1/2 myometrial invasion • Serous adenocarcinoma, clear-cell adenocarcinoma and myometrial invasion • Spread to the uterine adnexa, serosa, or cardinal ligament Invasion of the vaginal wall • Pelvic or para-aortic lymph node metastasis • Vesical or rectal invasion • Peritoneal dissemination • Distant metastasis	• Pelvic and/or para-aortic lymphadenectomy should be considered • Strength of recommendation: Grade C1
Institut National du Cancer (INCa) guidelines [17] **2011**	• Endometrioid adenocarcinoma G3 and ≥ 50% myometrial invasion • Tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma features.	• Para-aortic lymphadenectomy should be considered • Pelvic lymphadenectomy is optional • Pelvic and/or para-aortic lymphadenectomy should be considered
Collège national des gynécologues et obstétriciens français [82] **2017**	• High-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma features.	• Para-aortic lymphadenectomy should be considered • Pelvic lymphadenectomy

Similarly, there is no international consensus on the definition and anatomic extent of comprehensive PALND in terms of anatomical limits or how many LNs to remove. Neither of the two large RCTs comparing laparoscopic staging for EC with laparotomy explicitly explored the feasibility of laparoscopy for systematic LN dissection, especially for the more challenging PALND [53,54]. Moreover, the cephalad border of the P-PAL was generally limited to the inferior mesenteric artery (IMA). Worldwide, the extent of nodal assessment differs substantially between countries and surgeons. The updated ESMO-ESGO-ESTRO consensus guidelines for EC recommend that systematic PALND should include the infrarenal area [1,55]. A recent RCT comparing two surgical techniques – robot-assisted laparoscopic surgery versus laparotomy – in women with HR early-stage EC, reported equivalent numbers of removed paraaortic LNs, both above and below the IMA raising the issue of the anatomical limits [56].

In this setting, it is important to underline that between 15% to 25% of women with HR-EC have pelvic LN metastases and 5% to 15% have aortic LN metastases [18,20,36,48,57]. Hence, most women have negative LNs, and therefore systematic aortic and pelvic lymphadenectomy represents a surgical overtreatment, resulting in unnecessary morbidities and cost [20,36,45,57–59]. The role of FDG PET/ CT, which can detect the metabolic signal of actively growing cancer cells, has been investigated to improve selection of patients who can really benefit from systematic PALND. One systematic review and meta-analysis, showed that PET/CT demonstrated good performance for detecting LN metastases, with an overall accuracy, positive likelihood ratio, and negative likelihood ratio of 89.5%, 10.465, and 0.399, respectively [60]. In the National Comprehensive Cancer Network Guidelines version 1.2015, PET/CT is recommended among the preoperative staging procedures of serous or clear cell adenocarcinoma and carcinosarcoma, and according to the American College of Radiology Appropriateness Criteria (2014), is the most appropriate diagnostic technique (rating 9/9) for assessing lymphadenopathy in high-grade FDG-avid tumors [4].

Conversely, the role of SLNM, especially for HR histology, is currently being determined including the sites of injection (cervical vs hysteroscopic). However, interest in this technique is growing, as the goal of SLNM is to accurately identify lymphatic drainage to select the LNs that are most likely to harbor disease while also reducing the morbidity associated with systemic lymphadenectomy [61]. In a prospective validation study in women with HR-EC, Soliman et al. specifically studied SLN biopsies [62] and found SLN biopsy alone accurately identified 95% of patients with positive LNs. When combined with side-specific LN dissection, the false negative rate was 4.3% and the false-negative predictive value, i.e. the likelihood of a missed positive node if the SLN was negative, was 1.4%. These findings support SLNM in HR-EC and validate the algorithm of the Memorial Sloan-Kettering that

Table 3
Guidelines for adjuvant therapies in HR EC.

Guidelines Year of publication	HR definition	Recommendation
ESMO-ESGO-ESTRO [1] **2015**	• Stage I endometrioid, grade 3 with deep myometrial invasion > 50%, regardless of LVSI status	1 **Surgical nodal staging performed, node negative** 2 Adjuvant EBRT with limited fields should be considered to decrease locoregional recurrence 3 Level of evidence: I Strength of recommendation: B 4 Adjuvant brachytherapy may be considered as an alternative to decrease vaginal recurrence 5 Level of evidence: III Strength of recommendation: B 6 Adjuvant systemic therapy is under investigation 7 Level of evidence: II Strength of recommendation: C 8 **No surgical nodal staging** 9 Adjuvant EBRT is generally recommended for pelvic 10 control and relapse-free survival 11 Level of evidence: III Strength of recommendation: B 12 Sequential adjuvant chemotherapy may be considered to improve PFS and cancer specific survival (CSS) 13 Level of evidence: II Strength of recommendation: C 14 There is more evidence to support giving chemotherapy and EBRT in combination rather than either treatment modality alone 15 Level of evidence: II Strength of recommendation: B
National Comprehensive Cancer Network® (NCCN®) [4] **2016**	• Stage IA endometrioid, < 50% deep myometrial invasion • Stage IB endometrioid, > = 50% deep myometrial invasion	1 **Adverse risk factors not present** 2 Grade 1: no treatment 3 Grade 2: observe or vaginal brachytherapy 4 Grade 3: observe or vaginal brachytherapy 5 **Adverse risk factors present** 6 Grade 1: observe or vaginal brachytherapy 7 Grade 2: observe or vaginal brachytherapy and/or EBRT 8 Grade 3: observe or vaginal brachytherapy and/or EBRT
		1 **Adverse risk factors not present** 2 Grade 1: observe or vaginal brachytherapy 3 Grade 2: observe or vaginal brachytherapy 4 Grade 3: observe or vaginal brachytherapy and/or EBRT 5 **Adverse risk factors present** 6 Grade 1: observe or vaginal brachytherapy and/or external beam radiation therapy (EBRT) 7 Grade 2: observeor vaginal brachytherapy and/or EBRT 8 Grade 3: EBRT and/or vaginal brachytherapy ± chemotherapy
The British Gynaecological Cancer Society (BGCS) guidelines [69] **2016**	• Stage IB endometrioid, grade 3	• Consider external beam radiation versus vaginal brachytherapy. • Consider adjuvant chemotherapy.
Society of Obstetricians and Gynaecologists of Canada [80] **2013**	• Stage IB endometrioid, grade 3	• Adjuvant EBRT with or without vaginal brachytherapy should be considered • Adjuvant chemotherapy may be considered as an option for selected patients (those with excellent functional status, no significant co-morbidities, or presence of poor prognostic factors)
Japan Society of Gynecologic Oncology guidelines [71] **2016**	• Endometrioid adenocarcinoma G3 and ≥1/2 myometrial invasion	• **No residual tumor** • Adjuvant EBRT • Adjuvant chemotherapy • **Residual tumor present** • Adjuvant EBRT • Adjuvant chemotherapy • Hormone therapy 0144278283

includes performing a side-specific pelvic lymphadenectomy when an SLN is not detected. On this topic, the USA NCCN guidelines validate the use of SLNM in HR-EC [63,64].

In this setting, Signorelli et al. [65] assessed the combination of PET/CT and SLN biopsy to determine LN status compared with PET/CT alone in HR-EC patients (G2 and deep myometrial invasion, G3, serous clear cell carcinoma or carcinosarcoma). Women with HR-EC were preoperatively staged by PET/CT to detect LN metastases greater than 5 mm and exclude distant metastases (as it is a whole-body imaging tool). Systematic PALD was then performed if PET imaging was positive with a view to debulking. Conversely, if the PET/CT was negative, an SLN biopsy and ultrastaging could be performed to define LN status more accurately. The potential benefit of this approach would be to reduce undertreatment due to false-negative imaging findings in a preoperative imaging assessment and reduce the frequency of systematic PALD, minimizing intraoperative or postoperative complications in women with frequent comorbidities (such as obesity) [18,20,36,66–68].

3.1.3. Adjuvant therapies

There is a persistent debate about the rationale of pelvic radiotherapy and adjuvant chemotherapy or combined modalities in the standard management of HR-EC [20,21,36,72–74]. As previously mentioned, women with HR-EC form a heterogeneous

group of patients characterized by a higher grade and stage of EC, deep myometrial invasion, LVSI, or non-endometrioid histology such as serous or clear-cell cancers. The current level of evidence for treatment modalities from literature is low [1].

This is not surprising as the published literature used to define intraoperative and adjuvant therapeutic decisions is difficult to interpret. Specifically for adjuvant therapies, studies sometimes include patients who have undergone: (i) comprehensive surgical staging; (ii) incomplete surgical staging or; (iii) exclusive clinical staging with FIGO stage I disease with no lymphadenectomy [20,21,36,72–74]. In addition, the FIGO staging system has changed, further muddying the interpretation of the results of previously published studies [75].

In general, this group is associated with an increased risk of pelvic recurrence and distant metastases that contribute to poor prognosis [1,8,13,24,27,31–33]. ECs are generally radio-sensitive and local relapse can be prevented by radiotherapy. In this setting, external beam pelvic radiotherapy (EBRT) has been demonstrated to be the standard therapy for high-risk patients to optimize pelvic control [20,21,36,72–74] (Table 3). However, although a significant improvement in the local relapse risk compared with observation alone was reported, no significant survival advantage has been demonstrated according to a Cochrane systematic review and meta-analysis [21]. Therefore, the addition of chemotherapy, or replacement of radiotherapy by chemotherapy, has been analyzed and found to be effective in several randomized trials [76].

The current ESMO-ESGO-ESTRO guidelines recommend a therapeutic approach taking into account several options for type 1 HR-EC according to the surgical nodal staging results [1]. Table 3 summarizes the current adjuvant strategies from European and worldwide guidelines specifically for women with type 1 HR-EC. In this setting, we recently suggested a new paradigm of management based on the implementation of predictive, personalized, preventive, and participatory models to overcome the current heterogeneity in management approaches [13,15,77,78]. We reported several tools that could be useful in clinical practice to accurately identify the subset of women with type 1 EC who had negative prognostic factors and for whom complete surgical staging and adjuvant therapies could be necessary [51,52,79].

At final, we added in Table 4 more specific results regarding the use of radiation therapy and chemotherapy according to the most updated trial on the subject (not published yet).

Table 4
Recent preliminary results for radiation and chemotherapy therapies.

Study and year of publication	Number of patient and Methodology	Population of interest	Main results
PORTEC-3 2017 [80]	- 686 women were enrolled between 2006 and 2013 - Radiotherapy (RT) (48.6 Gy in 1.8 Gy fractions) or chemotherapy and radiotherapy (CTRT) (two cycles of cisplatin 50 mg/m^2 in week 1 and 4 of radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 3-week intervals)	- Women with HREC (FIGO stage I grade 3 with deep myometrial invasion and/or LVSI; stage II or III; or serous/clear cell histology)	- Three- and five-year OS for CTRT vs. RT was 84.4% versus 83.9%, and 81.8% versus 76.7%; overall HR 0.79 [95% CI 0.57-1.12, p = 0.183]. - Three-year FFS was 79.7% (CTRT) versus 71.8% (RT), and at 5 years 75.5% versus 68.9%, overall HR for FFS 0.77 [0.58-1.03, p = 0.078]. - Patients with stage III EC had lower 5-year FFS and OS compared to stage I-II (FFS 63.9% vs 78.9%, p < 0.001, and OS 74.3% vs 83.1%, p = 0.003).
GOG 249 ClinicalTrials.gov Identifier: NCT00807768 **Not published**	- 601 women were enrolled with randomized trial comparing adjuvant external beam RT to the pelvis (PXRT) or vaginal cuff brachytherapy plus chemotherapy (VCB/C). - The PXRT group (n = 301 patients) received a median radiation dose of 45 Gray (Gy) delivered over five weeks through standard four-field radiation or intensity-modulated radiation therapy (IMRT). Patients with serous, clear-cell or stage II tumors were eligible for a vaginal cuff brachytherapy boost, and 35 percent of the cohort received this additional therapy. The VCB/C group (n = 300 patients) received either high-dose rate (HDR) or low-dose rate (LDR) brachytherapy followed by three cycles of chemotherapy including paclitaxel (175 mg/m 2 – 3 hour) and carboplatin (AUC 6 – 21 days).	- Stage I-IIA endometrial - carcinoma, with high- - intermediate risk factors - Stage IIB (occult) - endometrial carcinoma - (any histology), with or - without risk factors - Stage I-IIB (occult) - serous or clear cell - endometrial carcinoma, - with or without other risk - features	- No statistically significant increases in recurrence-free survival (RFS) or overall survival (OS) in the brachytherapy-chemotherapy arm. - Three-year OS rates were 91 percent for pelvic radiation and 88 percent for the brachytherapy-chemotherapy combination, but this difference was not statistically significant (p = 0.57).
GOG 258 ClinicalTrials.gov Identifier: NCT00942357 **Not published**	- 813 patients to one of the two treatment arms between June 2009 and July 2014, with 407 patients assigned to the C-RT arm and 406 assigned to the CT arm. - Open-label randomized phase III trial compared treatment cisplatin and tumor volume-directed radiation followed by carboplatin and paclitaxel for four cycles (C-RT) versus carboplatin and paclitaxel treatment for six cycles (CT).	- Serous or clear cell - endometrial carcinoma - Stage IA-IVA endometrial carcinoma	- The estimates for 5-year OS are 70% for the C-RT arm versus 73% for the CT arm. - Treatment with C-RT reduced the vaginal recurrence incidence at 5 years by 3% versus 7% in the CT arm (HR 0.36, 95% CI [0.16, 0.82]). Pelvic and para-aortic recurrences were also reduced in the C-RT arm (10%) compared with the CT arm (19%; HR 0.43, 95% CI [0.28, 0.66]). Distant recurrences, however, were more common with C-RT (27%) versus CT (21%; HR 1.36, 95% CI [1.00, 1.86]). - The combined modality regimen did not improve RFS compared to chemotherapy (HR 0.9, 95% CI [0.74,1.1]).

4. Conclusion

Management and therapeutic approach of women with HR-EC remains controversial and is a major issue for the healthcare system because of its increasing incidence in high-income countries. More efforts need to be put into accurate classification based on genomic characterization to promote trials that will improve patient selection for surgical and adjuvant treatment including targeted therapies.

5. Discussion

The current treatments for HR-EC are based on surgery, radiation therapy, brachytherapy, and chemotherapy, which may either be used alone or sequentially, in combination with other treatments depending on disease stage, histological grade and risk group.

The treatment strategy is complex for several reasons: (i) changes in, and discrepancies between, the various classifications that relate to surgical management, adjuvant therapies, and prognosis; (ii) changes in lymphadenectomy indications and modalities (SLNM, pelvic +/- paraaortic LN dissection); (iii) changes in adjuvant therapy based on data from randomized trials; and (iv) the emergence of studies on targeted therapies.

Despite the absence of level 1 evidence for HR-EC, therapy often exposes women to a high risk of side effects. There is a lack of evidence-based data to specifically assess the outcomes of women who received multimodal treatments because studies on HR-EC patients published to date are limited by a short follow-up, do not specify the percentage of HR-EC patients with more aggressive disease who received surgery and additional therapies, and/or do not stratify the outcomes (oncologic and functional) according to the type of treatment. Hence, specific trials are needed to establish the role of systematic P-PA lymphadenectomy, adjuvant therapies and targeted drugs in HR-EC.

According to Bendifallah et al. [81] LVSI status remains a strong prognostic factor in high-risk ECs associated with a higher recurrence rate and lower RFS and OS whatever the histological type and lymph node status. It could thus be considered in future trials to guide decision-making about adjuvant therapy in high-risk EC.

In the future, the combination of PET/CT and SLN biopsy should result in improved determination of LN status in HR-EC patients which could reduce the rate of surgical overtreatment as well as related morbidities and costs. This assessment needs to distinguish each high-risk subgroup of patients and take into account the high heterogeneity of these patient.

Ruscito et coll. [83] have shown that, in cervical and endometrial cancer, SLN by indocyanin green mapping seems to be equivalent to the combination of blue dyes and (99)TC in terms of overall and bilateral detection rates.

Improved understanding of the molecular and genetic basis of EC has resulted in the emergence of targeted therapies that inhibit angiogenesis and the cellular signaling pathways involved in cell growth and proliferation. However, simply identifying and targeting mutations by refining molecular characterization to customize therapeutic strategies, does not necessarily equate to treatment response because of tumor heterogeneity and complex feedback loops that may lead to 'escape' pathways. Among the many targeted agents investigated – namely, antiangiogenic and mTOR/PI3K pathway inhibitor agents – to date, none has resulted in a change in clinical practice in HR EC. Hence, an effort has to be made to better identify the subset of patients who are more likely respond to these treatment approaches, the biomarkers that are likely predictive of response, and the combinations of therapies that are effective with acceptable toxicity.

In this context, although the past decade has witnessed the emergence of several remarkable clinical, pathologic, molecular, and imaging prognostic factors, there is room for improvement in individual patient risk assessment. Individualized patient care may be improved by the integration of individualized medicine, where each woman with EC would benefit from an individualized and customized treatment approach

Currently, the clinician needs to consider imaging techniques, surgical options, new adjuvant drugs, and the patient's quality of life, as well as, in the near future, genomic data. Such a combination of factors renders clinical decision making difficult, and even confusing, at the individual level. To overcome such limitations, a new paradigm has emerged that is based on the implementation of predictive, personalized, preventive, and participatory models. Various predictive tools (algorithms, nomograms, and risk scoring systems [RSS]) have been developed.

Hence, further studies are needed to validate to what extent such biomarkers can be applied to improve risk stratification and to tailor surgical and adjuvant treatment.

6. Five-year view

Endometrial cancer remains a management challenge, presenting with a full spectrum of disease ranging from patients with excellent prognosis to those with aggressive disease and poor outcome.

A well-designed, prospective and randomized controlled trial is required focusing exclusively on HREC patients taking account the high heterogeneity of each subgroup with a long follow up, especially to assess the therapeutic role of systematic lymphadenectomy and adjuvant therapies.

Improvements in the understanding of the molecular mechanisms of carcinogenesis is needed to help identify specific high-risk molecular signatures that could predict the biologic behavior of individual disease presentations and identify potential molecular candidates for targeted therapies. The major therapeutic challenge is to deliver adequate therapy while attempting to minimize treatment morbidity.

Key issues

- Endometrial cancer is a major cause of mortality for patients worldwide with nearly 200 000 cases diagnosed every year.
- The updated ESMO-ESGO-ESTRO guidelines address a new classification which defines a heterogeneous high-risk group of recurrence (HR-EC)
- High-risk factors are (combinations of) advanced age, high-grade, non-endometrioid histology, extensive lymphovascular space invasion, and more advanced disease stage.
- Guidelines on LN staging strategies in HR-EC are unclear and discordant. Controversy exists over indications and the therapeutic value of lymphadenectomy given the high heterogeneity of the patients who comprise this group and the low number of specific high-risk cases published in literature.
- To date, lymphadenectomy remains the standard technique to assess the lymphatic spread of EC leading many authors to stress the importance of identifying metastatic disease in women with HR-EC to accurately select candidates for adjuvant treatment.

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