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Adjuvant treatment of endometrial cancers: systematic review and perspectives

Abstract

The various adjuvant treatments to be proposed for endometrial cancers, alone or in combination are external beam radiotherapy (EBRT), vaginal brachytherapy (VBT), chemotherapy, targeted therapies and/or immunotherapy. In our systematic review, we will attempt to detail the various therapeutic indications, taking into account the latest technical advances and the inclusion of molecular factors in the new classification.

Endometrial cancer is very common gynecological tumor in developed countries, due to increasing life expectancy. Generally discovered at the localized stage (70%), the standard treatment remains surgery, including total hysterectomy with bilateral salpingo oophorectomy and lymph node dissection or sentinel biopsy of pelvic +/- para-aortic nodes. The choice of adjuvant treatment depends essentially on clinico-pathological risk factors. Recently, a new molecular classification has identified 4 subgroups with different prognoses to be taken into account when choosing adjuvant treatments.

Keywords: endometrial cancer, adjuvant treatment, chemotherapy, radiotherapy, molecular profile

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in countries with high life expectancy, notably North America. Global disparities were observed with a high frequency among white women but high mortality in black women. The American cancer society had reported an absolute difference rates of 21% at 5 years with 84% of White women surviving compared with 63% of Black women.[1] Over the last years, its incidence has increased in developed countries (130% in 30 years) with a parallel considerable mortality (1.9% per year on average).[2,3] Oncologically, there are three stages: localized; the most common (65-70%), locally advanced (15-20%) and metastatic (less than 10%).[4] According to SEER data, overall 5- year survival is around 82% for all stages combined.[4] Generally sporadic, but also hereditary in 5-10% of cases as part of Lynch syndrome in young women with usually microsatellite instability.[5] The standard primary treatment is surgery combining total hysterectomy with bilateral spapingo ovariectomy and pelvic

+/- para-aortic lymph node dissection. Sentinel lymph node biopsy is currently more widely used than dissection because of its low postoperative morbidity, particularly lymphedema.[6] In 2023, FIGO staging of endometrial cancer are up-date according to many advances in the understanding of the pathologic and molecular features (Table 1).[7]

Table 1 2023 FIGO staging of cancer of the endometrium

Stage	Description
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIB1	Metastasis or direct spread to the vagina and/or the parametria
IIIB2	Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both

Table 1 Continued...

Stage	Description
IIIC1	Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIIC1ii Macrometastasis
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	Metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

EEC: endometrioid carcinoma; LVSI: lymphovascular space involvement.

The indication for adjuvant treatment is based on the ESMO-ESGO-ESTRO 2016 consensus, according to the presence of prognostic factors: histological subtype, FIGO stage, grade, lymph node involvement and the presence or absence of lympho vascular invasion (LVSI) (Table 2).[8]

Table 2 ESMO-ESGO-ESTRO 2016 consensus, risk groups

Risk group	ESMO-ESGO-ESTRO consensus
Low risk	Endometrioid endometrial cancer
	Grade 1–2
	<50% myometrial invasion
	Lymphovascular space invasion negative
Low-intermediate risk	Endometrioid endometrial cancer
	Grade 1–2
	≥50% myometrial invasion
	Lymphovascular space invasion negative
High-intermediate risk	Endometrioid endometrial cancer
	Grade 3
	<50% myometrial invasion
	Any lymphovascular space invasion
	Endometrioid endometrial cancer
	Grade 1–2
	Lymphovascular space invasion unequivocally positive
	Any myometrial invasion
High	Endometrioid endometrial cancer
	Grade 3
	≥50% myometrial invasion
	Any lymphovascular space invasion
	Stage II–III endometrioid endometrial cancer
	No residual disease
	Non-endometrioid endometrial cancer stage I–III (serous, clear cell, or undifferentiated carcinosarcoma)
Advanced/metastatic	Stage III with residual disease and stage IVa
	Stage IVb

ESGO, European Society of Gynecological Oncology; ESMO, European Society for Medical Oncology; ESTRO, European Society

Recently, molecular biology has individualized four subgroups according to The Cancer Genome Atlas Research Network (TCGA): POLE ultra-mutated, mismatch repair deficient (MMRd), p53 abnormal and non-specific molecular profile (NSMP).[9] This brand-new molecular classification has proven to have predictive value and serves as the foundation for new trials.

Analysis of 373 cases (303 endometrioid carcinomas and 66 serous carcinomas) from The Cancer Genom Atlas (TCGA) comprehensive platform assessment identified 4 genomic sub-classes using a combination of whole genome or exone sequencing, microsatellite instability (MSI) assays, and copy number alterations. A novel ultramutated subtype (>100 mutations/megabase) with pathogenic variations in the exonuclease domain of DNA polymerase epsilon

(POLE)-ultramutated (POLEmut), hypermutated (10-100 mut/Mb) microsatellite-unstable, somatic copy number-high with frequent pathogenic variants in TP53 and somatic copy number-low with frequently phosphoinositide 3-kinase (PI3K) abnormalities (Table 3).[9]

Table 3 ESMO-ESGO-ESTRO 2016 consensus, risk groups

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

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

Approximately 5–15% of EC carry one of these pathogenic POLE mutations. These POLEmut EC are found in relatively early-stage but high-grade tumors with prominent lymphovascular infiltration.[10,11] POLEmut carcinomas are associated with an exceptionally favorable prognosis with very low relapse incidence regardless of adjuvant treatment.[9–12] The mismatch-repair deficient (dMMR) is more often referred to the group with microsatellite instable group (MSI) detected in immunohistochemistry. The dMMR sub-group comprises about 25–30% of all EC and is defined by the loss of nuclear expression of one or more mismatch repair proteins and caused by somatic events such as MLH1 or PMS2 promoter hypermethylation but also due a germline mutation in one of the mismatch repair genes (Lynch syndrome). The dMMR sub-group has an intermediate prognosis and a strong immunogenic response.[13]

The third molecular sub-group (5-15% of EC) consists of EC with frequent occurrence of TP53 mutations, but a high number of somatic copy number alterations and a relatively low somatic mutation rate.[14] This group comprises mainly high-grade EC and non-endometrioid histologies (serous, carcinosarcoma and clear cell cancers). The p53-abn groupe occur a poor prognosis due to aggressive growth with early spread of disease. The fourth and most commun sub-group of EC (30-40%), with no specific molecular profile (NSMP), has both a low mutational burden and low number of somatic copy number alterations. Prognosis in these tumors is stage dependent, but can be considered as intermediate risk. This sub-group typically contains endometrioid carcinomas with positive staining for estrogen and progesterone receptors.[9]

In some cases, about 3–6% have more than one classifying alteration and are referred to as multiple- classifier endometrial cancers. Vermij et al. has established the diagnostic algorithm for the classification ofthe four molecular sub-groups (Figure 1).[15]

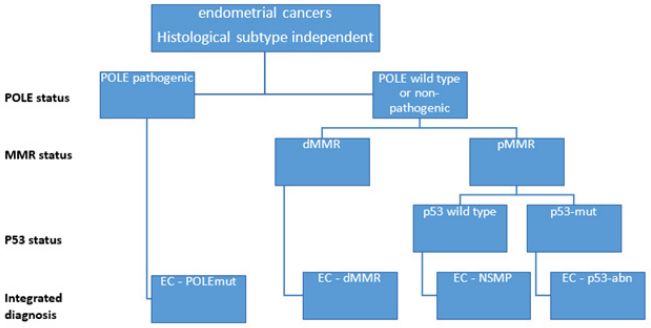

Figure 1 Diagnostic algorithm for the integrated molecular EC classification.

Low risk group

This group includes stage I endometrial cancers, grade 1-2, infiltrating < 50% of the myometrium and without lymphovascular invasion, according to the ESMO classification. In the Sasada trial, the 5-years overall survival (OS) was 97.9% and 5-years recurrence rates were 2.6%.[16] No OS benefits have been shown and local recurrence can be treated with radiotherapy.[17] The PORTEC 1/2 trials had identified a POLE mut subgroup (5-15% of EC) as a favourable prognostic factor independently of other clinico- pathological parameters.[18,19] Further, patients with stage I-II/POLE mut are considered low risk and do not require adjuvant treatment. For stage III, no data are available and observation may be proposed as an option.[20]

Intermediate risk group

The Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) 1 and Gynaecologic Oncology Group (GOG) 99 trials

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demonstrated that adjuvant pelvic radiotherapy significantly reduced the risk of locoregional recurrence, without improving distant recurrence-free survival (DRFS) or overall survival (OS).[21,22] Further, another randomized trial (ASTEC/EN.5) also demonstrated this benefit without impacting OS.[23] The majority of recurrences occur in the vaginal vault (75%) in case of post-operative observation. In the PORTEC-1 trial, radiotherapy and vaginal brachytherapy for localized vaginal recurrence achieved 3 and 5-year survival rates of 73% and 65% respectively, and complete remissions of almost 90%. However, locoregional pelvic recurrence or distant metastatic disease shown poor 3-year survival rates (8-14%).[17–24]

In the PORTEC-2 trial, vault brachytherapy (VBT) had the same disease-free and overall survival rates as pelvic external beam radiotherapy, but a lower rate of local vaginal recurrence (1.6% vs 1.8%) and, above all, less gastrointestinal toxicity.[25] In the European Society of Medical Oncology (ESMO) recommendations, omitting the VBT can be proposed for patients >60 years, referring to the Danish trial (14% locoregional recurrence risk but the same OS).[26,27] This option should be discussed on a case-by-case basis after concertation with patients. Patients with stage IA non-endometrioid EC or p53 abnormal are considered in the intermediate group. This subgroup has never been evaluated in randomized trials, and the benefit of pelvic radiotherapy or VBT is unclear. Simple observation or adjuvant treatment should be discussed in tumor boards.

High intermediate risk group

According to PORTEC 1 and GOG-99, it includes stage I endometrioid, grade 3 (<50% myometrial invasion, regardless of LVSI) or stage I endometrioid, grade 1-2, unequivocally positive LVSI (regardlessof depth of myometrial invasion). Long-term results of the PORTEC-2 trial showed no difference in vaginal recurrence rate (3.4% EBRT vs 2.4% VBT, p=0.55) and OS (69.5% EBRT vs 67.6% VBT). However, the risk of pelvic recurrence was higher with VBT than EBRT (6.3% vs. 0.9%, p=0.004).[28] Unfavourable factors risk of pelvic recurrence defined by significant LVSI, TP53 abnormality, and L1 cell- adhesion molecule (L1CAM) expression may benefit from pelvic EBRT.[28] Subgroup analysis of the MMR status of 197 patients with high intermediate risk found that MMR deficient increased the risk of recurrence(14.1% vs. 3%, p=0.003) and significantly reduced 5-year recurrence-free survival (73.5% vs. 95%, p=0.004).[29] Based on the new TCGA molecular classification, the PORTEC-4a trial will identify patients who could benefit from either observation, VBT or escalation by EBRT.[30] In the phase III GOG-249 trial, substituting pelvic EBRT by VBT plus carboplatin/paclitaxel chemotherapy over four cycles in this group of patients and/or stage I-II serous (15%) or clear cell (5%) cancers was unsuccessful in achieving the primary endpoint of 5-RFS (76% vs 81%, p=0.31) as well as OS (87% vs 85%, p=0.57). Acute side effects grade ≥ 2 were higher in the VBT and chemotherapy combination arm (94% vs. 44%).[31] Result analysis by stage of the PORTEC-3 trial, which evaluated concomitant and adjuvant chemotherapy with radiotherapy versus exclusive EBRT, showed small benefit in stage I-II non-serous (5-year OS 2% and FFS 4%).[32] Therefore, pelvic EBRT is the standard treatment for high intermediate risk; adjunction of chemotherapy should discussed by case considering side effects.

High-risk group

Heterogeneous group according to clinical stage, histological type and, more recently, molecular subtype. Itincludes endometrioid carcinomas stage I grade 3 with myometrial infiltration and/or lymphovascular invasion; endometrioid stage II-III and non-endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma) cancers stage I-III. Currently, stage III-IVA endometrioid EC without residual disease or stage I-IVA p53-abnormal are all considered high-risk EC. The risk of recurrence is high, ranging from 21 to 23%. Three main trials have evaluated the benefits of combined chemotherapy and radiotherapy treatment in this high-risk group (PORTEC-3, GOG-249 and GOG-258). Updated results from the PORTEC-3 trial at 6 years, comparing the addition of chemotherapy concomitantly and then adjuvant to radiotherapy versus EBRT alone, showed a 5% benefit in OS and 7% in FFS. The benefit was clearly higher in the serous and stage III subgroups. Clear-cell cancers have a worse prognosis, (only 5% ofpatients in the PORTEC-3); the frequency of recurrence in this subtype (especially wild-type p53) was similar to patients with endometrioid tumors but significantly lower than serous cancers.[32] In GOG-249, theevaluation of the superiority of VBT with chemotherapy compared with pelvis EBRT for high intermediate-risk (according to GOG-33 criteria) and high risk (endometrioid stage II or serous/clear cell stage I-II) was negative. No benefit in recurrence-free survival or OS whatever the histological type.[31]

Recently, the phase III open label trial GOG-258, tested whether association of EBRT at 45 Gy and 6 months of platinum chemotherapy (Cisplatin Days 1-29 and 4 cycles od adjuvant Paclitaxel/Carboplatine) is associated with longer relapse-free survival than chemotherapy alone (6 cycles of Paclitaxel/Carboplatine) in 818 EC patients with stage III-IVA. After 47 months of follow-up, no difference in 5 years-RFS (59% in the chemoradiotherapy group and 58% in the chemotherapy-only group). Chemoradiotherapy was associated with a lower 5-year incidence of vaginal recurrence (2% vs. 7%) and pelvic and paraaortic lymph-node recurrence (11% vs. 20%). Distant recurrence was morecommon in association with chemoradiotherapy but no statisticly significative (27% vs. 21%; hazard ratio

= 1.36). Adverse events grade 3 or more were higher in in the chemotherapy-only group (63% vs 58%). Taking into consideration all of this trials, concomitant or sequential chemoraditherapy is the recommendedtreatment for high-risk EC.[33]

Two new studies have demonstrated the benefits of immunotherapy in combination with chemotherapy in locally advanced EC. The first trial used an anti-PD1 drug in 494 patients with locally advanced stage III- IV or first reccurent EC; 23.9% of whom were mismatch-repair deficient (dMMR) and microsatellite instability-high (MSI-H). Dostarlimab was administered concomitantly with 6 cycles of paclitaxel and carboplatin, then as maintenance for 3 years. In the dMMR-MSI-H population, the 24-months PFS was higher in the dostarlimab arm than placebo (61.3% vs 15%, HR = 0.28, p<0.001). Same benefit in the globa population (24-months PFS : 36.1% vs 18.1%). OS at 2 years is clearly superior with dostarlimab (71.3%) than placebo (56%). Adverse events are increased with immunotherapy but remain manageable.[34]

The second trial, NRG GY018/Keynote-868 using Pembrolizumab in 816 EC patients with measurable disease (stage III or IVA) with paclitaxel plus carboplatin. The patients were stratified into two cohorts according to whether they had mismatch repair-deficient (dMMR) or mismatch repair-proficient (pMMR) disease. the second trial, using Pembrolizumab in 816 EC patients with measurable disease (stage III or IVA) in combination with paclitaxel plus carboplatin. The patients were stratified into according to whether they had mismatch repair-deficient (dMMR) or mismatch repair-proficient (pMMR) disease. One-year Progression-free survival in the dMMR cohort were 74% in the pembrolizumab group and 38% in the placebo group. In the pMMR cohort, median progression-free survival was 13.1 months

with pembrolizumab and 8.7 months with placebo. Acute adverse events of immutherapy and chemotherapy were also manageable.[35] Therefore, the addition of immunotherapy should be discussed on a case-by-case at the multidisciplinary committee.

It is necessary to show the value of adjuvant chemotherapy treatment for each subgroup in light of the new molecular classification and its strong prognostic value. Regardless of the histological subtype, EC patients with p53-abn have a worse prognosis, according to analysis of PORTEC-3 tissue samples. Patients with POLEmut, have a good prognosis. In treatment, patients with p53-abn benefited from adjuvant radio- chemotherapy regardless of clinical stage or histological type, while those with POLEmut had excellent survival and could benefit from de-escalation.

In conclusion, adjuvant therapy for endometrial cancer is based not only on clinico-pathological risk factors, but also on molecular profiles with precise prognostic values, enabling personalized precision medicine. Four molecular subgroups have been identified by TCGA, enabling postoperative treatment to be tailored to the prognostic risk of local and/or distant progression. Adjuvant chemotherapy combined with radiotherapy has been shown to be beneficial for the p53-abn subtype, while the POLEmut has better recurrence-free survival and OS, so therapeutic de-escalation may be the standard, with the same results and fewer toxicities. The dMMR subtype seem to benefit more from adding immunotherapy to chemotherapy, while NSMPs have a moderately higher disease-free survival rate with radio-chemotherapy. Therefore, it's very important to select adjuvant therapies carefully, incorporating the new molecular classification into our decisions to improve therapeutic and prognostic outcomes. A program of trials has already been left RAINBO in high-risk EC patients, which will compare different therapeutic protocols according to molecular subclasses: for p53-abn ECs, the comparison will be between radio-chemotherapy with or without the addition of PARP inhibitors; for patients with a non-specific molecular profile, bi- therapy with radio-chemotherapy will be compared with other modalities such as chemotherapy alone or hormonal therapy; for POLE-mut patients, observation will be compared to adjuvant treatment with EBRT or VBT; and finally for dMMR patients, the benefit of immunotherapy with radiotherapy has yet to be demonstrated. Certainly, the results of these series of studies will have a real impact on the decision- making process for adjuvant treatment in the years to come.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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