Adjuvant treatment for endometrial cancer

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Purpose of review
This article reviews and interprets studies on adjuvant treatment of endometrial cancer published during the last 18 months.

Recent findings
For patients with intermediate and high intermediate risk endometrial cancer, vaginal brachytherapy remains the adjuvant therapy of choice. New molecular markers might help to define patients in this group for whom observation only is sufficient and women who might have benefitted from external beam radiotherapy. Preliminary results from large randomized controlled trials have shown that in early stage, high-risk endometrial cancer the addition of chemotherapy to external beam radiotherapy (EBRT) did not improve survival. The combination of vaginal brachytherapy with three courses of chemotherapy resulted in similar progression-free and overall survival (3 years) as EBRT. In stage III high-risk endometrial cancer, the addition of chemotherapy to EBRT improved failure-free survival but not overall survival (immature data). Chemotherapy alone had the same efficacy concerning progression-free and overall survival (immature data).

Summary
Three large randomized clinical trials on the role of adjuvant radio and/or chemotherapy have so far provided only immature results. Discussions about changes of clinical practice should be postponed until mature data from all three trials are available. The impact of new molecular markers for risk stratification will be assessed in ongoing RCTs.

Keywords
chemotherapy, endometrial cancer, immunotherapy, molecular markers, radiotherapy

INTRODUCTION

Endometrial cancer is the 4th most common malignancy in females in industrialized countries [1,2]. For the United States, 61 880 new cases and 12 160 related deaths are estimated for 2019 [1]. Death rate rose from 2012 to 2016 by 2.1% per year on average [1]. In Germany, as an example for a West-European industrialized country, 10 600 new cases and 2600 deaths of endometrial cancer have been estimated for 2018. The incidence rate decreased slightly, whereas both, the crude and adjusted mortality rates, have remained constant for the last years [2]. Although there might be slight geographical differences in the epidemiology of endometrial cancers, the prognosis of this disease is quite favorable with 5-year disease-specific survival rates of about 80% (all stages) [1,2], because of the fact that the majority of endometrial cancer is diagnosed in early stages, where 5-year relative survival rates are about 95% [1]. Twenty percent of endometrial cancer patients, however, die of their disease due to aggressive tumors, advanced disease at diagnosis, or both. Patients with high risk of recurrence and death have traditionally been offered adjuvant radiotherapy after surgical management for many decades [3,4]. Recent trials have relativized the impact of adjuvant radiotherapy on survival of patients with high-risk endometrial cancer [3,4]. As most patients that die of endometrial cancer, succumb to extraperitoneal disease, adjuvant chemotherapy has been added to the treatment for locally advanced endometrial cancer or cases with aggressive histological type [3,4]. A number of randomized trials have addressed this issue with debatable results [3,4].

The review will briefly describe the current recommendations for adjuvant treatment of endometrial cancer. It will summarize the studies that have been published on this topic during the last 18 months, and try to incorporate these new

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KEY POINTS

- About 20% of endometrial cancer patients die of their disease.
- For patients with intermediate and HIR endometrial cancer, adjuvant vaginal brachytherapy remains the standard of care.
- New molecular risk factors might help to define patients with intermediate and HIR who need no adjuvant radiotherapy at all and women who need external beam radiotherapy instead of brachytherapy.
- At present, the preliminary results of three landmark prospective randomized trials suggest an increasing role of adjuvant chemotherapy.
- The data are still immature and do not allow for a clear differential indication of chemotherapy, radiotherapy, their combination, and sequence.

findings in recommendations for treatment and the design of future trials.

CURRENT STANDARD OF CARE

Different systems of risk classifications have been used in the randomized controlled trials on adjuvant therapy of endometrial cancer which makes comparisons difficult [3,4]. A recent, widely accepted risk group classification based on histological findings has been defined by the European Society of Medical Oncology (ESMO)–European Society of Gynecological Oncology (ESGO)–European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines for endometrial cancer (Table 1) [5].

These guidelines provide also various differentiated recommendations for adjuvant therapy in various scenarios, including observation, vaginal brachytherapy (VBT), external beam radiotherapy (EBRT), chemotherapy, and combinations of these treatment modalities [5].

RECENT DEVELOPMENTS

Studies reported during the last 18 months have focused on three topics:

(1) Evaluation of new prognostic factors and definition of prognostic subgroups.
(2) Assessment of the efficacy of adjuvant radiotherapy in early stage endometrial cancer of HIR and high risk.
(3) Evaluation of adjuvant radiotherapy or chemotherapy or the combination of both treatment modalities in high-risk endometrial cancer.

NEW PROGNOSTIC FACTORS AND PROGNOSTIC SUBGROUPS

Based on the findings from the Cancer Genome Atlas (TCGA) [6], four distinct molecular subclasses of endometrial cancer based on genomic architecture and mutational burden were defined: p53 abnormal, based on mutant like immunostaining (p53abn), mismatch repair deficient, based on mismatch repair protein expression (MMRd), presence of polymerase E exonuclease domain hotspot mutation (POLE) and nonspecific molecular profile (NSMP) in which none of these aberrations were present. Retrospective analysis of 381 patients with

Table 1. Risk groups to guide adjuvant therapy (ESMO–ESGO–ESTRO consensus guidelines for endometrial carcinoma) [reproduced with permission from [5]]

Risk group	Description
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative
Intermediate	Stage I endometrioid, grade 1–2, >50% myometrial invasion LVSI negative
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion regardless of LVSI status Stage I endometrioid, 1–2, LVSI unequivocally positive, regardless of depth of invasion
High	Stage I endometrioid, grade 3, >50% myometrial invasion, regardless of LVSI status Stage II Stage III, endometrioid, no residual disease Non endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)
Advanced	Stage III residual disease and stage IVA
Metastatic	Stage IVB

FIGO 2009 staging used, molecular factors were considered but not included; tumor size was considered but not included. *LVSI*, Lymphvascular space invasion. FIGO, International Federation of Gynecology and Obstetrics; ESGO, European Society of Gynecological Oncology; ESMO, European Society of Medical Oncology; ESTRO, European Society for Radiotherapy and Oncology.

grade 3 endometrioid endometrial cancer revealed that these tumors are a mixture of molecular subtypes of endometrial cancer rather than a homogenous group. POLE-mutated tumors of G3 and stage I had excellent prognosis, MMRd and NSMP an intermediate, and p53abn poor prognosis [7▪▪].

This molecular classifier, called 'Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)' was further validated retrospectively in another cohort of 452 endometrial cancer patients and is considered to be ready for clinical evaluation through prospective clinical trials [8].

L1 cell-adhesion molecule (L1CAM) had been shown to be a significant indicator of high-risk disease in endometrial cancer. Combining ProMisE and L1CAM analysis relevant L1CAM staining was found in 80% of p53 abnormal tumors and in 8% of NSMP endometrial cancers. L1CAM positive endometrial cancers of NSMP had a worse prognosis and had more often International Federation of Gynecology and Obstetrics (FIGO) grade 3 and high FIGO stage (II–IV) [9].

A group of leading gyneco-pathologists has put into perspective the new developments. In the context of the Endometrial Cancer Project of the International Society of Gynecological Pathologists, they have analyzed and evaluated the prognostic algorithms and resulting adjuvant therapy determinations proposed by National Comprehensive Cancer Centre Network and ESMO and the new molecular classifier. They have come to the conclusion that the molecular classification of endometrial cancer that has emerged from the Cancer Genome Atlas (TCGA) study provides additional, potentially superior prognostic information to traditional histologic typing and grading. This classification does not, however, replace the other clinicopathologic risk assessment including depth of myometrial invasion, cervical, vaginal, serosal surface, adnexal, and parametrial invasion and lymphovascular space invasion. It is envisaged that molecular and clinicopathologic prognostic grouping systems will likely work better together [10▪▪].

A retrospective cohort analysis of 16 851 patients from the National Cancer Database with endometrial cancer of FIGO stage IA–II showed that positive peritoneal cytology was associated with decreased survival even in low-grade endometrioid endometrial cancer. Use of adjuvant chemotherapy in women with positive cytology was associated with increased survival [11].

The 10-year results of the Postoperative Radiation Therapy in Endometrial Cancer (PORTEC)-2 trial for high-intermediate risk endometrial cancer confirmed that VBT is the standard adjuvant treatment for this group of endometrial cancer patients [FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or FIGO 1988 stage 1B (<50% myometrial invasion) with age greater than 60 and grade 3; or FIGO 1988 stage 2A (endocervical glandular involvement, with any age, except for grade 3 with deep invasion)].

Ten-year pelvic recurrence was more frequent in the VBT group than in patients who received adjuvant EBRT. Vaginal recurrence, distant metastases, and overall survival after 10 years were not significantly different between the groups. Retrospective pathology review and molecular analysis showed that L1CAM and p53-mutant expression and substantial lymphovascular space invasion were high-risk factors for pelvic recurrence and distant metastasis. EBRT provided better pelvic control in patients with unfavorable risk factors [12▪▪].

In the currently ongoing PORTEC-4a trial, women with stage I–II endometrial cancer with high intermediate risk (HIR) features are randomized to receive standard vaginal brachytherapy or adjuvant treatment directed by their integrated molecular risk profile. The molecular profile stratifies patients into favorable (about 50%), who will be observed, intermediate risk (about 45%), who will receive brachytherapy, and an unfavorable group (about 5%), who will receive EBRT [12▪▪].

ADJUVANT RADIOTHERAPY ALONE IN HIGH INTERMEDIATE AND HIGH-RISK ENDOMETRIAL CANCER

A series of studies analyzed data from the National Cancer Data Base trying to ascertain the efficacy of adjuvant radiotherapy in stage I and II endometrial cancer.

Data from 132 976 FIGO stage 1 endometrial type endometrial cancer patients treated surgically were stratified by PORTEC-based low, low-intermediate, high-intermediate, and high-risk groups. On multivariate analysis patients with high-intermediate risk and high risk experienced improved 5 and 10-year survival with adjuvant radiotherapy (46% VBT alone; 45% EBRT alone; 9% EBRT + VBT). There was no survival benefit for adjuvant radiotherapy among patients at low or low-intermediate risk [13].

A group of 5711 patients with FIGO pT1a, N0 or NX endometrial cancer of clear cell, papillary serous, or carcinosarcoma histology was analyzed, of which 29.5% received VBT. Overall survival (3 years) was significantly increased by VBT, even after propensity score adjustment. Similar results were seen whether tumors were confined to endometrium or had less than 50% myometrial invasion [14].

To assess the effect of adjuvant radiation therapy without chemotherapy on survival of women with stage II endometrioid endometrial cancer, the data

of 2681 patients were analyzed. Simple hysterectomy had been performed in 84%. Five-year overall survival was 80% (EBRT), 87% (VBT), and 83% (EBRT + VBT), suggesting that VBT alone may be a reasonable adjuvant radiotherapy modality for properly selected women with stage II endometrial cancer with adequate lymph-node dissection and low-grade tumors [15].

Analyzing data from 2877 patients with stage II endometrioid endometrial cancer from the Surveillance Epidemiology, and End Results (SEER) database, it was found that adjuvant radiation, whether delivered by brachytherapy or EBRT is associated with improved disease-specific survival in patients with high-grade tumors, indicating that brachytherapy may be sufficient [16].

ADJUVANT RADIOTHERAPY AND/OR CHEMOTHERAPY IN HIGH-RISK ENDOMETRIAL CANCER

Data from 6102 patients with stage II endometrial cancer from the National Cancer Database diagnosed between 2010 to 2013 showed that 6% received adjuvant chemotherapy alone after hysterectomy and bilateral salpingo-oophorectomy. Nine percent received chemo/radiotherapy (CRT), 31% radiotherapy alone, or 54% no adjuvant treatment. The presence of lymphovascular invasion and grade 3 disease was strongly associated with chemotherapy or CRT. Receipt of chemotherapy (alone or with radiotherapy) was not associated with an overall survival advantage compared with radiotherapy alone [17].

A retrospective chart review from 414 patients who underwent hysterectomy for FIGO IA endometrial cancer with serous, clear cell, or mixed histology between 2004 and 2015 showed that adjuvant radiotherapy and chemotherapy were associated with better local control and disease-free survival. Observation may be appropriate in patients who have adequate surgical staging [18].

A total of 11 746 patients with FIGO stage IB and II endometrial cancer with either serous, clear cell or grade 3 endometrial adenocarcinoma diagnosed between 2004 and 2012 were identified. The addition of adjuvant chemotherapy to radiation was associated with improved 5-year overall survival (OS) [19].

The efficacy of adjuvant therapy in patients with clear cell endometrial cancer was assessed in 4298 cases (stages I–IVa) from the National Cancer Database treated from 1998 to 2011. After controlling for stage, comorbidity score, age, and other meaningful predictors of death, adjuvant therapy was not associated with decreased risk of mortality [20].

A total of 1789 patients with stages I–III serous ($n = 1437$) or clear cell ($n = 352$) endometrial cancer were identified from SEER-Medicare Databank. Four-year cancer-specific mortality was analyzed suggesting a benefit of brachytherapy in stages I–II serous/clear cell cancers, a benefit of chemotherapy in stage III serous, clear cell cancers, and a benefit of chemotherapy and brachytherapy in stages I–II serous cancers [21].

To evaluate the survival benefit of adding VBT to pelvic EBRT in women with stage III endometrial cancer, analysis of data from 12 988 patients from the National Cancer Data Base (2004–2013) showed that the addition of VBT to EBRT was associated with an improvement in survival for women with endocervical or cervical stromal invasion [22].

Reassessing the value of platinum-based adjuvant chemotherapy in serous endometrial cancer in patients from a single center, it was suggested that vaginal brachytherapy improves PFS in stage I tumors whereas the added value of chemotherapy remained uncertain. Most patients treated with platinum-based chemotherapy who had microscopic residuum had recurrences within 2 years (across stages) [23].

To assess the optimal adjuvant treatment sequence for node-positive endometrial cancer 1826 patients with stage IIIC1 to IIIC2 from the National Cancer Data Base were analyzed. The study suggests that upfront chemotherapy followed by radiotherapy may be a better treatment sequence for adjuvant therapy in women with advanced endometrial cancer [24].

To define the role of lymphadenectomy (LND) and adjuvant therapy in patients with uterine carcinosarcoma, data from 1140 cases from two large Dutch databanks were analyzed. LND was related to improved survival when more than 10 nodes were removed. Adjuvant therapy (radiotherapy or chemotherapy or radiochemotherapy improved survival when LND was omitted or when nodes were positive [25].

The PORTEC-3 trial, an international multicenter randomized phase 3 trial, investigated the benefit of adjuvant chemotherapy during and after radiotherapy versus pelvic EBRT alone for women with high-risk endometrial cancer. Final results were now reported on 660 eligible patients after a median follow-up of 60.2 months (Table 2). After adjustment for stratification factors, 5-year overall survival was not significantly improved by the addition of chemotherapy: 81.8% (95% CI 77.5–86.2) with additional chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy alone (adjusted hazard ratio 0.76; 95% CI 0.54–1.06; $P = 0.11$), whereas 5-year failure-free survival was improved: adjusted hazard ratio: 0.71 (0.53–0.95); $P = 0.022$. In subgroup analysis, effects of additional chemotherapy on failure-free survival were significant in stage III but not

Table 2. Recent randomized controlled trials on adjuvant treatment of endometrial cancer

	Patients	Treatment	Toxicity	Recurrence	Overall survival
PORTEC-3 [26▪▪]	Endometrioid endometrial cancer, stage 1A, grade 3 + LVSI; stage IB, G3; stage II–IIIC; serous and clear cell endometrial cancer, stages I–III $n = 686$	48.6 Gy + 2 × cisplatin 50 mg/m^2 followed by 4 × carboplatin AUC 5 + paclitaxel 175 mg/m^2 versus EBRT alone VBT boost allowed in both arms	Acute: 60 versus 12% neuropathy (≥grade 2); at 3 years: 8 versus 1%	Failure-free survival after 5 years: 75.5 versus 68.6%; adjusted hazard ratio: 0.71, $P = 0.022$; no difference for stage I and II (80.8 versus 76.6%), $P = 0.47$	81.8 versus 76.7%, adjusted hazard ratio: 0.76, $P = 0.109$, interim data
GOG-249 [28▪▪]	FIGO I–II endometrioid endometrial cancer, high intermediate risk or serous and clear cell endometrial cancer $n = 601$	VBT + 3 × carboplatin AUC 6 + paclitaxel 175 mg/m^2 versus EBRT (44–54 Gy) ± VBT boost	Acute: 64 versus 11% late: 12 versus 11%	At 3 years, 82% recurrence free in both groups	At 3 years, 87% (VBT + chemotherapy), 81% (EBRT)
GOG-258 [29▪▪]	Endometrioid endometrial cancer, stage III or IVa, residual tumor <2 cm or serous/clear cell endometrial cancer, stage I–II and positive cytology $n = 813$	EBRT (volume directed) ± VBT + 2 × cisplatin 50 mg/m^2 followed by 4 × carboplatin AUC 6 + paclitaxel 175 mg/m^2 versus 6 × carboplatin AUC 6 + paclitaxel 175 mg/m^2	Acute: 30 versus 26%, 75% patients completed study therapy in C-RT arm compared with 85% in chemotherapy arm	Recurrence-free survival at 5 years: hazard ratio: 0.9 (95% CI 0.74–1.1) distant recurrence 27 versus 21% hazard ratio: 1.36 (95% CI 1.00–1.86); vaginal recurrence hazard ratio 0.36; pelvic/paraaortic recurrence hazard ratio 0.43	70% (C-RT) versus 73% chemotherapy (immature data)

AUC, area under curve; *EBRT*, External beam radiotherapy; GOG, gynecologic oncology group; *LVSI*, lymphvascular space invasion; PORTEC, postoperative radiation therapy in endometrial cancer; *VBT*, vaginal brachytherapy.

in stage I and II patients. It should be emphasized that the addition of chemotherapy had the same positive effects on overall and failure-free survival in serous and clear cell endometrial cancers as in endometrioid cancer. Toxicity during therapy was more common in the chemoradiation arm. Neuropathy (grade 2 or worse) persisted more often after chemoradiotherapy than after radiotherapy. Though declared as 'final results' data on OS were immature in this analysis [26▪▪].

In a different article, the PORTEC group published the results of central pathology review by expert gynecopathologists performed before randomization for the PORTEC-3 trial. Histological type, grade or other items changed in 43% of women with high-risk endometrial cancer leading to ineligibility for the trial in 8% [27▪].

Gynecologic Oncology Group (GOG)-249 study, a randomized phase III trial that has not yet been fully published, compared conventional EBRT and VBT followed by three cycles of chemotherapy in women with high-risk stage I–II endometrial cancer. Three-year relapse-free and overall survival as well as the number of vaginal recurrences and distant metastases were not significantly different in both arms. VBT and chemotherapy led to more pelvic and paraaortic recurrences and had greater acute toxicity. The frequency of long term toxicity was similar in both arms (Table 2) [28▪▪].

Another pivotal randomized trial, GOG-258 examined the effect of adding EBRT to chemotherapy alone which was considered to be standard adjuvant treatment in stage III or IVa endometrial cancer with postoperative residual tumor less than 2 cm or patients with stage I or II and clear cell or serous histology and positive cytology. Of 737 eligible patients randomized, 714 had stage III disease. The addition of radiotherapy did not improve recurrence-free survival: hazard ratio 0.9 (95% CI 0.74–1.1) which was the primary endpoint of the trial. Distant recurrences at 5 years were more common in the combined modality arm (27%) as compared with chemotherapy alone (21%) (hazard ratio = 1.36; 95% CI 1.00–1.86). The addition of radiotherapy was, however, associated with an impressive reduction in pelvic and paraaortic recurrence (10 versus 19%; hazard ratio = 0.43) as well as reduction in vaginal recurrence (3 versus 7%; hazard ratio 0,36). Overall survival data are not yet mature (C-RT: 70%; chemotherapy: 73%) (Table 2) [29▪▪].

NEW APPROACHES FOR SYSTEMIC TREATMENT

No trials on new approaches for adjuvant systemic treatment have been published during the last year, but two studies on palliative treatment of recurrent/advanced endometrial cancer are of potential relevance for adjuvant therapy. In a phase II study run by the GOG (GOG-86P) frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, and ixabepilone/carboplatin/bevacizumab were tested in patients ($n = 349$) with advanced/recurrent endometrial cancer. PFS was not increased in any experimental arm compared with historical controls [30].

In 61 patients with advanced/recurrent serous endometrial cancer that overexpressed HER2/neu, a randomized phase 2 trial was performed to assess the effect of adding trastuzumab to carboplatin/paclitaxel. The addition of trastuzumab was well tolerated and significantly increased PFS (hazard ratio 0.44; 90% CI = 0.26–0.76) [31]. This study was declared by the American Society of Clinical Oncology to be one of the most relevant clinical advances of the year 2019 [32].

After the demonstration of activity of pembrolizumab in heavily pretreated endometrial cancer patients with programmed death ligand-1-positive tumors [33] an intensive evaluation of this new immunotherapeutic approach will take place. The relevance of immune environment versus molecular subtype to predict response to immunotherapy needs clarification [34].

CONCLUSION

For low-risk endometrial cancer observation alone remains the procedure of choice after surgical therapy. Further research will have to evaluate whether additional molecular markers such as L1CAM may identify patients with high risk of recurrence among this group with seemingly good prognosis [9].

For patients with intermediate and HIR, VBT has been confirmed as the adjuvant treatment of choice by the 10-year results of the PORTEC-2-trial. The integration of the new molecular markers might allow for observation alone in about 50% in these HIR patients and help to identify the few patients with a distinctly higher risk that might benefit from EBRT. This topic is addressed by the ongoing PORTEC-4a trial [12▪▪].

For patients with high-risk endometrial cancer, three landmark RCTs have been performed [26▪▪,28▪▪,29▪▪]. So far, only preliminary results have been published. Though a lot of speculations have been offered and discussions in the community are spirited, no definite conclusion can be drawn from these immature data.

We have no results showing that EBRT is superior to VBT and chemotherapy in stage I and II HIR [28▪▪]. We have data that chemoradiation might be superior to EBRT in stage III endometrial cancer [26▪▪] but chemotherapy alone might be equivalent or superior to the chemoradiation [29▪▪]. A point that has been so far neglected in major RCTs is the optimal sequence of chemo and radiotherapy. In many tumor entities, for example, breast cancer, adjuvant chemotherapy, addressing disseminated tumor cells, is performed prior to radiotherapy, the latter improving primarily local control. Though we have performed adjuvant radiotherapy in endometrial cancer almost for a century, and have added chemotherapy only recently, it might be useful to design trials starting with chemotherapy [24]. The mature results of the large RCTs will help to define the relevance of chemo and radiotherapy. Probably, additional trials will be necessary to define the optimal sequence and combination of the different modalities and the implementation of the new molecular-based risk classification.

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Conflicts of interest

There are no conflicts of interest.

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