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REVIEW

Adjuvant therapy for high-risk endometrial cancer: recent evidence and future directions

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ABSTRACT

Introduction: Although the majority of women with endometrial cancer have a favorable prognosis due to early symptoms, 15–20% have high-risk disease features and are at increased risk of recurrence. In order to improve prognosis for these patients, several trials have compared chemotherapy (CT), radiotherapy (RT) or the combination of CTRT.

Areas covered: This review focuses on the current evidence on adjuvant treatment for women with high-risk endometrial cancer and future perspectives.

Expert commentary: For stage I-II high-risk endometrial cancer, external beam radiotherapy ensured good local control and no significant benefit in progression-free or overall survival was found with the addition of chemotherapy in 2 recent randomized trials. For women with stage III disease, the combination of chemotherapy and radiotherapy improved progression-free survival with a non-significant improvement of overall survival. Adjuvant chemotherapy alone resulted in higher rates of pelvic and para-aortic recurrence. More toxicity and reduced quality of life were found during and after adjuvant CTRT. It is essential to discuss the benefits and disadvantages of chemotherapy and radiotherapy with individual patients for shared decision-making. Translational research is ongoing to further characterize individual tumors, identify sensitivity to (immuno)therapies and find new treatment targets to improve outcomes.

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Endometrial cancers; risk factors; radiotherapy; chemotherapy; adjuvant treatment; systematic review

1. Introduction

1.1. Background

Endometrial cancer (EC) is the most common gynecological cancer in developed countries and primarily affects postmenopausal women between 60 and 85 years of age, with a median age at diagnosis of about 65–76 years. Women with EC often have comorbidities such as cardiovascular diseases, diabetes, hypertension, and obesity. The incidence of EC has been increasing in the past decades due to ageing of the population and increased rates of obesity. The estimated number of uterine cancers diagnosed in the United States in 2018 is 63,000, and the estimated number of endometrial cancer-related deaths is about 11,000, reflecting the fact that the majority of patients have a favorable prognosis. This is largely because most women present with early-stage disease due to early symptoms of vaginal bleeding [1–3].

1.2. Risk classification

As most (75–80%) of patients with endometrial cancer present with early disease, risk factors have been defined by which those with stage I EC are subdivided in low-risk, intermediate-risk, and high-risk disease. Adjuvant treatment for women with stage I EC is based on the major risk factors histological grade, depth of myometrial invasion, age, and lymph-vascular space invasion (LVSI) [4]. Patients with low-risk disease, about 50% of all EC cases, are those with stage I endometrioid type EC, grade 1–2, with less than 50% myometrial invasion, and without LVSI. These women have a very favorable outcome (95% recurrence-free survival at 5 years) and can be treated with surgery alone. Several large randomized trials have shown that for patients with (high-) intermediate risk EC, adjuvant radiotherapy significantly reduces the risk of vaginal and pelvic recurrence, but without overall survival benefit [5–7]. The majority of locoregional recurrences (75%) were located in the vaginal vault, and most could be cured with radiotherapy at the time of recurrence, with 73% and 65% 3- and 5-year survival rates after recurrence [8]. The indication for RT became limited to those with high-intermediate risk factors, as these patients had about 20% locoregional recurrence with surgery alone, which was reduced to 5% with adjuvant external beam RT (EBRT) [9]. Subsequently, the PORTEC-2 trial was initiated to investigate the role of vaginal brachytherapy as compared to EBRT for women with high-intermediate risk endometrial cancer. PORTEC-2 showed high efficacy of vaginal brachytherapy in reducing vaginal recurrence of endometrial cancer, with similarly high vaginal control rates in both arms (98%). As fewer side effects and better health-related quality of life (HRQOL) were reported with vaginal brachytherapy as compared to

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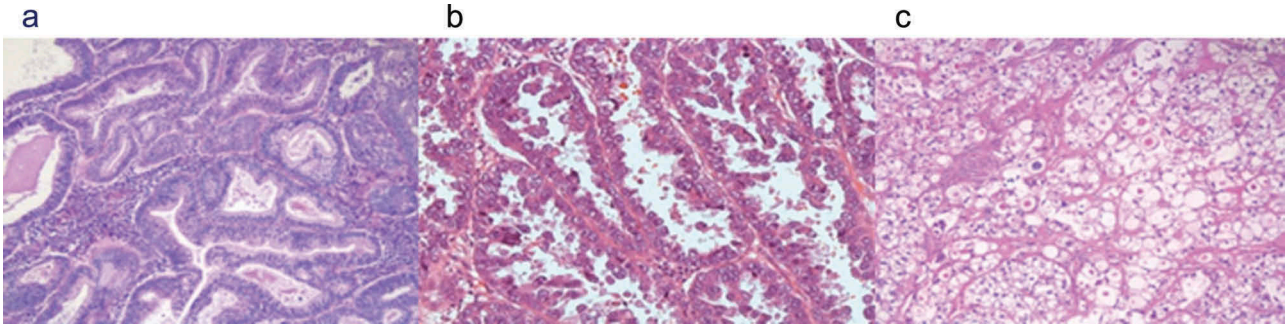

Figure 1. Hematoxyline-eosine (HE) coupes: endometrioid (a), serous (b) and clear cell (c) endometrial cancer.

EBRT, vaginal brachytherapy became the standard adjuvant treatment for women with high-intermediate risk EC [10,11].

About 15–20% of all women with EC are diagnosed with high-risk endometrial cancer (HREC), which comprises endometrioid endometrial cancer (EEC) stage I, grade 3 with outer 50% myometrial invasion or with lymph-vascular space invasion (LVSI); stage II or III EEC; or stage I-III with non-endometrioid (serous or clear cell) histologies (Figure 1). Higher incidence rates of distant metastases and endometrial cancer-related death have been reported for women with HREC [12–15]. Serous and clear cell cancers have a higher risk of aggressive intra-abdominal spread and a poorer prognosis. However, when diagnosed at an early stage, similar survival rates have been reported for serous and clear cell EC as compared to grade 3 EEC [16].

The staging and histological classification systems for EC have been updated in the past decades, which makes it difficult to compare previous trials [17]. Definitive staging according to the International Federation of Gynecology and Obstetrics (FIGO) staging system is based on surgical and pathology findings. The most recent FIGO staging was published in 2009, which replaced 1988 FIGO staging [18].

Based on the results of the large randomized trials, risk groups have been defined which were found to have the highest risk of recurrence among women with early disease stages. The high-intermediate risk groups defined in the GOG#99 and PORTEC-1 trials had the common risk factors of age, grade and depth of invasion, with different cutoffs; GOG#99 also included LVSI. A more recent risk group classification has been defined in the ESMO-ESGO-ESTRO consensus guidelines for EC (Table 1) [4].

Table 1. Risk groups to guide adjuvant therapy (ESMO-ESGO-ESTRO consensus guidelines for endometrial carcinoma)[4].

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, grade 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. LVSI: lymph-vascular space invasion.

1.3. Surgical staging

Standard surgery for EC consists of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TAH/TLH + BSO). Laparoscopic surgery is to be preferred in early-stage tumors, as randomized trials showed no difference between abdominal or laparoscopic approaches in risk of complications, disease-free and overall survival. However, improved short-term quality of life, shorter hospital stay, less pain, and quicker resumption of daily activities were reported after the laparoscopic procedure [19–23].

There is considerable controversy whether a pelvic and/or para-aortic lymphadenectomy should be performed. Two large randomized trials have been published which found no difference in progression-free or overall survival rates when comparing surgery with and without lymphadenectomy [24,25]. A retrospective study of 671 patients with EC treated in two different centres which did or did not use para-aortic lymphadenectomy suggested that extensive pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy alone for patients with intermediate or high risk of recurrence [26]. However, no prospective, randomized evidence for para-aortic lymphadenectomy is available, while the Italian trial included 26% of patients who had both pelvic and para-aortic lymphadenectomy and did not find differences in outcome. Patients who undergo a pelvic and/or para-aortic lymphadenectomy are more likely to develop surgery-related toxicities, mainly lymphedema. A meta-analysis assessing 1922 patients reported a higher risk (RR 8.39) of lymphedema or symptomatic lymphocyst formation in patients who underwent a lymphadenectomy [27]. Several trials showed increasing rates of leg edema with increasing number of lymph nodes dissected, independent of the use and type of adjuvant therapy [28,29].

As most of the trials cited above included a large majority of women with early stage, low-intermediate risk disease, there is still lack of evidence on the value of lymphadenectomy to direct adjuvant treatment in high-risk disease. The international STATEC trial has recently started accrual in the United Kingdom, Australia, and New Zealand, and randomizes women with stage I grade 3 EC to surgery with or without lymphadenectomy. In the group treated without

lymphadenectomy, adjuvant chemotherapy and/or radiotherapy will be given based on final histology. In the group with lymphadenectomy, adjuvant treatment will be based on lymph node evaluation and final pathology diagnosis. Women with stage I-II disease who are node negative will receive no additional treatment apart from vaginal brachytherapy. Patients with lymph node involvement and/or otherwise stage III disease will receive adjuvant chemotherapy and radiotherapy. A substudy on the role of sentinel node will be performed in the group with lymphadenectomy [30].

The sentinel node procedure has become part of standard surgery and has been proven safe to replace lymph node dissection in various tumor types such as breast cancer, melanoma, and vulvar cancer. Although some trials have reported on the sensitivity and specificity of the sentinel node procedure in EC, sentinel lymph node evaluation in EC is less straightforward than in breast cancer and vulvar cancer, where the sentinel node is usually represented by 1 or 2 nodes. In EC, up to about eight sentinel nodes can be found bilaterally, most often in the iliac region but less frequently also at other sites, including the para-aortic region. Furthermore, in view of the low risk of disease spread in the majority of patients with early stage disease, the exact role of sentinel node procedure is still unknown.

First trials of the sentinel node procedure including ultrastaging have shown a high degree of diagnostic accuracy in detecting macroscopic and microscopic lymph node metastases. Detection of isolated tumor cells poses a new clinical challenge, as these are not considered true metastases in most tumor types. Sentinel node biopsy has the potential to fully replace lymphadenectomy and spare patients the associated morbidity of extensive lymph node dissection, especially lymphedema [31,32].

1.4. Pathology evaluation

Reproducibility of the pathology diagnosis is essential, as adjuvant treatment is based on high-risk pathology criteria. Previous studies of pathology review by expert subspecialty pathologists, however, have shown that discrepancies with and without consequences for adjuvant treatment frequently occur. Evaluation of female reproductive tract pathology had the highest rates of discrepancies between original and review pathology assessment [33], and a Canadian study reported EC as the tumor site with most frequent differences in pathological assessment [34]. In another Canadian cohort discrepancies with consequences for adjuvant treatment were reported in 8% of all biopsies and hysterectomy specimens taken together. Retrospective pathology review was performed in the PORTEC-1 and 2 trials, which showed that 24% and 14%, respectively, of patients were in retrospect ineligible for the trials, mainly based on shifts in tumor grading with low reproducibility of the intermediate grade [6,9,10]. In the PORTEC-3 trial, upfront pathology review was done to include only truly high-risk patients in the trial. Analysis of pathology review in the Netherlands and the UK (48% of PORTEC-3 participants) revealed that 8% of patients did not fulfill the eligibility criteria after central pathology review. These patients did not enter the trial, which ensured a true high-risk trial population and prevented lower-risk patients from unnecessary toxic treatment [35].

High rates of disagreement between observers have been reported for histological grade and type. Previous studies have shown that binary grading assessing high versus low grade should be preferred, as the reproducibility of grade 2 is limited [36–38]. For assessment of histological type, a previous study has shown that the consensus can be increased by the use of immunohistochemical (IHC) markers. With a panel of three IHC markers (TP53, ER and CDKN2A) consensus was reached in 96% of cases, compared with 72% without the use of IHC [39].

Molecular analysis will further improve diagnostic accuracy and risk assignment. Traditional classification used to categorize EC into two pathogenetic types that were primarily based on clinical, metabolic and endocrine characteristics: type I and type II EC [40]. Type I cancers were endometrial type, estrogen-dependent tumors of low grade and typically occurring in relatively younger women, while type II cancers were estrogen-independent, more often of non-endometroid type and/or high tumor grade, occurred in older women, and had an unfavorable prognosis.

In 2013, the Cancer Genome Atlas (TCGA) research network has conducted an extensive molecular genetic analysis of EC. They defined four molecular subtypes of EC based on mutational burden and copy number alterations, with clear prognostic difference: *POLE* ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high groups [41]. This risk classification has been validated in several EC cohorts [42,43].

Previous studies reported substantial LVSI, L1 cell adhesion molecule (L1CAM) expression and beta-catenin (*CTNNB1)* mutation as strong independent prognostic factors for recurrence and overall survival [15,44–46]. Furthermore, single biomarker studies have identified several molecular alterations with prognostic relevance [47,48].

Translational analysis in the PORTEC 1 and 2 patients integrated the molecular subgroups proposed by the TCGA, with results of a multigene mutation analysis, other established biomarkers and LVSI. Integrating these clinicopathological and molecular risk factors showed an improved risk assessment in the PORTEC 1 and 2 trial cohorts [43]. This integrated risk assessment is now being prospectively tested in the PORTEC-4a trial [49].

2. Methods

2.1. Data sources and study selection

The aim of this review was to provide an overview of the current treatment modalities for high-risk endometrial cancer (excluding carcinosarcoma). We searched PubMed for clinical studies published in English between 1 January 1980, and 27 March 2018, with the terms 'endometrial cancer' AND 'radiation therapy' AND 'chemotherapy' AND 'survival' OR 'failure free survival'. The search identified 539 papers. After selection of the title, abstract and full text eight relevant publications of prospective trials (1 phase II trial and 7 phase III trials) were included for this review. In addition, we included recently presented abstracts of two relevant randomized trials.

3. Treatment modalities

3.1. Chemotherapy compared with radiotherapy alone

Pelvic external beam radiation therapy (EBRT) has been standard adjuvant treatment for women with HREC for many decades, although there is a paucity of evidence on improvement of survival. Randomized trials have compared adjuvant chemotherapy alone (CT) with pelvic EBRT alone [50–52]. Table 2 shows an overview of prospective phase III trials investigating adjuvant chemotherapy in high-risk endometrial cancer.

A Japanese trial [50] randomized 385 patients with stage IC-III endometrial cancer (EC) to adjuvant EBRT or three cycles of cyclophosphamide 333mg/m2, doxorubicin 40mg/m2 and cisplatin 50mg/m2 (CAP) chemotherapy every 4 weeks. No significant differences in progression-free and overall survival were observed. Five-year overall survival rates were good in both treatment arms, 85% (EBRT) vs. 87% (CAP), reflecting that approximately 60% of patients had stage IC disease and 85% had grade 1–2 tumors. It was suggested in an unplanned subgroup analysis that women with high-risk factors (n = 120) defined as stage IC patients with either age over 70 or with grade 3 endometrioid adenocarcinoma or stage II/IIIA (positive cytology) disease, might have benefited from chemotherapy, but this was not found for stage III disease.

In the Italian trial [51], 345 patients with high-risk EC (HREC) were randomized to EBRT or five cycles of cyclophosphamide 600 mg/m2, doxorubicin 45 mg/m^2 and cisplatin 50mg/m2 (CAP) chemotherapy every 4 weeks. Sixty-five percent of patients had stage III disease and 56% of patients had a grade 3 endometrioid tumor. EBRT delayed pelvic recurrence and chemotherapy delayed distant metastases, but no differences in overall and progression-free survival were found: 5-year OS was 69% (EBRT) vs. 66% (CAP) and 5-year PFS was 63% vs. 63%. In these two trials, only women with endometrioid tumours were included.

In the GOG-122 trial [52], patients with advanced stage disease (stage III and IV EC, residual macroscopic disease ≤2 cm allowed) were randomized to receive whole-abdominal irradiation (WAI) or chemotherapy (eight cycles of doxorubicin 60 mg/m2 and cisplatin 50 mg/m2). Chemotherapy significantly improved overall survival (55% vs. 42%). However, event rates were similar (54 vs. 50%) and 5-year rates of pelvic recurrence were 18% for chemotherapy and 13% for RT. Substantial grade 3–4 toxicity occurred in patients treated with chemotherapy, and significantly higher rates of peripheral neuropathy were reported after treatment by patients treated with AP chemotherapy [53].

Relatively large multicentre and single centre retrospective studies reported higher rates of pelvic recurrence if high-risk patients were treated without RT, supporting the continued use of locoregional radiotherapy in patients undergoing adjuvant chemotherapy [54–56].

3.2. Combination of chemotherapy and radiotherapy compared with radiotherapy alone

Because increased pelvic relapse has been reported with chemotherapy alone, the combination of EBRT with chemotherapy has been explored in both retrospective and prospective studies [54–56]. A first small randomized trial was the GOG-34 trial [57], in which 181 patients with high risk stage I-II EC were randomized to RT with or without single-agent doxorubicin. No difference in overall and progression-free survival was found, although due to protocol violations, small sample size, and substantial number of patients lost to follow-up, the authors concluded that the trial failed to determine the effect of the addition of sequential doxorubicin.

In a phase II trial (RTOG 9708) among women with HREC, the combination of EBRT with two concurrent cycles of cisplatin 50 mg/m2 on days 1 and 28, followed by four adjuvant cycles of cisplatin 50 mg/m2 and paclitaxel 175 mg/m2 was tested in 46 patients, resulting in favorable 4-year overall and disease-free survival rates of 85% and 81%, respectively [58]. A completion rate of 98% was reported. Acute grade 3 and grade 4 adverse events were reported in 12 (27%) and 1 (2%) patient during concurrent chemotherapy, respectively, and in 9 (21%) and 26 (62%) patients during adjuvant chemotherapy. Chronic grade 3 and 4 adverse events were reported in 7 patients (16%) and 1 patient (2%) [59].

In a phase III trial led by the Nordic Society of Gynecological Oncology (NSGO) with participation by the European Organization for the Research and Treatment of Cancer (EORTC), the NSGO9501/EORTC55991 trial, EBRT alone was randomly compared with EBRT either preceded or followed by four cycles of platinum-based chemotherapy. The trial population comprised 378 evaluable women, mainly with stage I EC (91%); 60% had endometrioid type EC, 20% had serous cancer and 17% clear cell histology. Various chemotherapy schedules and sequences were used; the majority of patients (83%) received doxorubicin or epirubicin 50 mg/m2 with cisplatin 50mg/m2, but other schedules were allowed. Most patients received radiotherapy before chemotherapy, but 17% received chemotherapy first. The results of this trial were published in a pooled analysis with the unfinished ManGO Iliade III trial (n = 156). The ManGO Iliade III trial randomly allocated patients with stage IIB-III endometrioid type EC to EBRT with or without sequential chemotherapy, given before radiotherapy. Chemotherapy consisted of three cycles of doxorubicin 60 mg/m2 and cisplatin 50 mg/2, given every 3 weeks. 65% of women had stage III disease.

The pooled analysis of these two trials reported on a total cohort of 534 patients and showed improved progression-free survival (HR 0.63; 95% CI 0.44–0.89; p = 0.009) and a trend for improved overall survival (HR 0.69; 95% CI 0.46–1.03; p = 0.07) with the addition of chemotherapy to EBRT [60].

A meta-analysis by the Cochrane collaboration suggested a small benefit (4%) in progression-free survival and overall survival after platinum-based adjuvant chemotherapy, irrespective of radiotherapy. Radiotherapy reduced pelvic recurrence (RR 1.28; 0.97–1.68). Although the analysis of pelvic recurrence was underpowered, chemotherapy was found to be less effective in reducing pelvic recurrence than radiotherapy [61].

A small Finnish trial [62] randomized 156 patients to either EBRT alone or EBRT given in a sandwich regimen (CTRT) with three cycles of cisplatin 50mg/m2, epirubicin 60mg/m2 and cyclophosphamide 500mg/m2. Radiotherapy was given in two courses

of 28 Gy in 14 fractions each, separated by a 3-week treatment break, in which chemotherapy was given in the combined arm. Sixty-six percent of patients had stage I disease and 66% of patients had grade 1–2 tumors. No difference was found in overall survival ($p = 0.77$). Recurrences were reported in 18% (RT) vs. 23% (CTRT, ns), and more serious toxicity occurred in the chemotherapy arm.

In these trials, no clear survival benefit of combined chemotherapy and radiotherapy was found, while various chemotherapy schedules and sequences were used, and no data on late toxicity or quality of life were provided. Therefore, the rationale for the PORTEC-3 trial was to investigate the benefit of combined adjuvant treatment for women with HREC cancer using a uniform treatment schedule, starting both treatments early, and with thorough toxicity and quality of life analysis.

In the PORTEC-3 trial [63], patients with HREC were randomized to pelvic radiotherapy with or without concurrent and adjuvant chemotherapy. The PORTEC-3 treatment schedule was based on the RTOG 9708 trial [58], with substitution of cisplatin with carboplatin in the adjuvant phase, as this was at the time the established treatment for recurrent or metastatic disease with a more favorable toxicity profile [64]. Two cycles of concurrent cisplatin 50mg/m2 were given in week 1 and 4 of radiotherapy. Adjuvant chemotherapy consisted of four cycles of carboplatin AUC5 and paclitaxel 175mg/m2, given every 3 weeks. Patients had a median age of 62 years and 98% of patients had performance score 0 or 1. Thirty-nine percent of patients had grade 1–2 endometrioid EC (EEC), 28% had grade 3 EEC and 25% had serous or clear cell cancers. The overall survival was good (79% at 5 years) considering the high-risk disease population in this trial, and a non-significant OS improvement of 5% was found for patients in the combined treatment arm: 82% in the CTRT arm, vs. 77% in the RT arm; HR 0.76, $p = 0.11$. A significant 7% improvement of failure-free survival was found for patients in the CTRT arm: 76% vs. 69%, HR 0.71, $p = 0.022$. The benefit in FFS was mainly found among stage III patients, who have a higher baseline risk of recurrence. For stage III EC, an 11% FFS improvement was found with CTRT (69% vs. 58%, HR 0.66, $p = 0.014$), compared with only 4% for women with stage I-II disease.

The large majority of recurrences were distant recurrences (22% in the CTRT arm, versus 29% for RT; 21% were isolated distant recurrence and about 6% had combined distant and vaginal/pelvic recurrence). Isolated vaginal and/or pelvic recurrence was very rare (1% CTRT vs. 2% RT).

Significantly more and more severe physician reported acute toxicity was found in the combined treatment arm, with grade ≥3 toxicity reported for 60% vs. 12%; these were mainly hematological, GI and bone, joint and muscle-related pain AE. In the first year after randomization the patients recovered well, although 1–3 years after treatment more grade 2 toxicity was reported for patients treated with CTRT (24 vs. 18% at 3 years, $p = 0.03$),without significant differences in grade ≥3 toxicities. The only persisting significant difference in grade 2 toxicity between the two treatment arms was sensory neuropathy, which was reported in 10% vs. 1% after 1 year, and in 9% vs. 0% at 3 and 5 years. The difference in acute toxicity was also reflected in patient-reported health-related quality of life (HRQL). During treatment and in the first 6 months after treatment a decreased quality of life was found in general HRQL and in all EORTC functioning scales. The rapid recovery in the first 6 months after treatment was reflected in the functioning scales as well, and at 1 and 2 years after treatment there were no significant differences, except for a small but significant difference in physical functioning. This might be related to the increased rate of sensory neuropathy in the combined treatment arm, as tingling or numbness was reported by 25% of patients after CTRT compared with 6% after RT at 2 years after treatment [65].

In the GOG-249 trial [66], 601 patients with high-intermediate or high-risk stage I-II EC were randomized to receive pelvic EBRT alone, or vaginal brachytherapy followed by 3 cycles of carboplatin AUC6 and paclitaxel 175 mg/m2 (VBT + CT). Eighty-nine percent had lymphadenectomy and 20% had serous cancer. Although the results have not yet been fully published, two presented abstracts with 3- and 5-year results showed that vaginal brachytherapy with chemotherapy was not superior to EBRT in terms of overall or progression-free survival. However, the rate of pelvic recurrences was significantly higher in patients treated with VBT + CT, and more acute toxicity was reported in this group. There were no differences in PFS by histological type. It was concluded that pelvic EBRT is still the standard of care for women with stage I-II EC with high-intermediate or high-risk factors.

3.3. Combination of chemotherapy and radiotherapy compared with chemotherapy alone

To determine the added value of radiotherapy to chemotherapy alone in women with stage III-IVA EC, the GOG-258 trial randomly assigned 813 women with stage III-IVA EC (97% stage III, 18% with serous cancers) to either pelvic EBRT with concurrent cisplatin and adjuvant carboplatin and paclitaxel (in the same schedule as used in the PORTEC-3 trial), or chemotherapy alone (six cycles of carboplatin AUC6 and paclitaxel 175 mg/m^2 given every 3 weeks) [67]. The results were presented at the 2017 ASCO annual meeting and showed overlapping recurrence-free and overall survival curves. Significantly more pelvic and para-aortic lymph node recurrences were reported in patients treated with chemotherapy alone: HR = 0.43 (CI: 0.28–0.66). Women treated with the combined schedule had a trend for more distant recurrence as the first failure (HR = 1.36 (CI: 1.00–1.86). It was not reported how many women with pelvic or para-aortic lymph node recurrence in the chemotherapy-alone arm had salvage radiotherapy.

4. Expert commentary

High-risk endometrial cancer is a very heterogeneous group of tumors, containing both early-stage endometrial cancer with high-risk disease characteristics, as well as more advanced stages EC and non-endometrioid tumors. For the total group of HREC women, two trials have reported a significant benefit in failure-free or progression-free survival with the addition of chemotherapy to radiotherapy, but with a non-significant improvement in overall survival [60,63]. If this group of

Table 2. Prospective phase III trials investigating adjuvant chemotherapy in high-risk endometrial cancer.

Trial	Enrollment	No. of patients	Eligibility	Randomisation	CT details	OS	RFS	Pelvic recurrence
Susumu et al (JGOG 2033)[50]	1994–2000	385	EEC, stage IC-IIIC, >50% MI	pelvic RT vs. CT	3x dyclofosfamide, doxorubicine + cisplatin	5 yrs: 85% vs. 87%	5 yrs: 84% vs. 82%	5 yrs: 7% vs. 7%
Maggi et al (GICOG)[51]	1990–1997	345	EEC, stage Ic G3, II G3 (>50%MI), stage III	pelvic RT vs. CT	5x dyclofosfamide, doxorubicine + cisplatin	5 yrs: 69% vs. 66%	5 yrs: 63% vs. 63%	5 yrs: 12% vs. 16%
Randall et al (GOG- 122)[52]	1992–2000	396	Stage III/IV, residual tumor ≤2cm	whole abdominal RT vs. CT	8x doxorubicine + cisplatin	5 yrs: 42% vs. 55%	5 yrs: 38% vs. 50%	5 yrs: 13% vs. 18%
Morrow et al (GOG- 34)[57]	1977–1986	181	Clinical stage I/II (occult), 31% N+	Pelvic RT vs pelvic RT+ CT	6-8x doxorubicine	No difference	No difference	NA
Kuoppala et al[62]	1992–1996	156	Stage IA–B G3 or IC–IIIA G1–3	Pelvic RT vs. pelvic RT+ CT	3x cisplatin, epirubicin + cyclophosphamide	No difference	5 yrs: 85% vs. 82%	5 yrs: 3% vs. 2%
Hogberg et al (NSGO/ EORTC)[60]	1996–2007	378	Stage I-III, stage I serous	Pelvic RT vs. pelvic RT + CT	Different schedules; 83% doxorubicine + cisplatin	5 yrs: 76% vs. 83%	5 yrs: 72% vs. 79%	NA
Hogberg et al (MaNGO ILIADE-III)[60]	1998–2007	156	Stage IIB, IIIA-C	Pelvic RT vs. pelvic RT + CT	Doxorubicin + cisplatin	5 yrs: 73% vs. 78%	5 yrs: 61% vs. 74%	NA
Pooled analysis[60]		534				5 yrs: 75% vs. 82%	5 yrs: 69% vs. 78%	5 yrs: 16% vs. 12%
de Boer et al (PORTEC-3)[63]	2006–2013	660	Stage I HR*, stage II-III or NEEC stage I-III	Pelvic RT vs. pelvic RT+ CT	2 x cisplatin concurrent +4 cycles adjuvant carboplatin + paclitaxel	5 yrs: 77% vs. 82%	5 yrs: 69% vs. 76%	5 yrs (total): 9.2% vs. 4.9%
Randall et al (GOG- 249)[66]	2009–2013	527	Stage I-II HR*, NEEC stage I-II	Pelvic RT vs. VBT+ CT	3x carboplatin + paclitaxel	3 yrs: 91% vs. 88%	3 yrs: 82% vs. 82%	3 yrs: 4.4% vs. 9.2%
Matei et al (GOG-258)[67]	2009–2014	736	Stage III/IVA* (residual tumor ≤2cm), Stage I+ II NEEC	Pelvic RT + CT vs. CT	RT + CT: 2 x concurrent cisplatin + 4 cycles adjuvant carboplatin + paclitaxel. CT: 6x carboplatin + paclitaxel	5 yrs: 70% vs. 73%	No difference	5 yrs: 10% vs. 19%

*FIGO 2009

CT: chemotherapy; RT: radiotherapy; VBT: vaginal brachytherapy; EEC: endometrioid endometrial cancer; NEEC: non-endometrioid endometrial cancer; OS: overall survival; pfs: progression-free survival; HR: high-risk; G: grade; MI: myometrial invasion; NA: not applicable.

patients is divided by stage, two trials [63,66] reported a good local control for stage I-II HREC after external beam radiotherapy alone. For this group of patients, the potential benefit of chemotherapy seems too limited in view of the increased toxicity during and after chemotherapy. For women with stage III EC who have a higher baseline risk of recurrence, a significant benefit in failure-free survival and trend for an improved overall survival was found in favor of the combination of chemotherapy and radiotherapy in the PORTEC-3 trial. When comparing combined chemotherapy and radiotherapy to chemotherapy alone, more vaginal, pelvic and para-aortal recurrences were reported in stage III/IV patients, while there was no difference in progression-free and overall survival between these two treatments [67].

Several study groups have performed subanalyses to determine the interaction between histology and treatment. In the combined analysis of the NSTO9501/EORTC55991 and Mango Iliade III trials, a significant effect on both failure-free and overall survival was found with the addition of chemotherapy for endometrioid tumors, while no effect was found for serous cancers [60]. In the PORTEC-3 trial a subgroup analysis found that serous cancers (>25% serous component) had significantly lower overall survival and failure-free survival than the other histological subtypes and at least as much effect from the addition of chemotherapy compared with all other histological types: failure-free was 58% (95% CI 42–70) with chemoradiotherapy, versus 48% (95% CI 34–61) with radiotherapy alone (HR 0.63, 95% CI 0.36–1.12; $p = 0.11$) [63]. The GOG evaluated the relation between histology and outcome in patients with advanced and metastatic endometrial cancer participating in first-line chemotherapy trials. One thousand two hundred and three patients in four randomized clinical trials were evaluated and no different effect of treatment was found for the various histological types [68].

It is important to note that different chemotherapy agents have been used in the various trials. In the combined analysis of the NSTO9501/EORTC55991 and Mango Iliade III trial and the GOG trial, platinum-based chemotherapy schedules were used and only 13%, 0%, and 24% received a taxane-based chemotherapy schedule, respectively. In the PORTEC-3 patients, all patients in the CTRT arm were treated with both platinum- and taxane-based chemotherapy. This may have improved efficacy for serous cancers.

A better understanding of the risk groups may improve clinical decision-making for HREC patients and reduce over- and under-treatment. The Cancer Genome Atlas Group (TCGA) provided a molecular classification of EC with a clear correlation with progression-free survival [41]. This molecular classification has been validated in intermediate risk EC tumors. To explore whether HREC tumors can be classified in the TGCA molecular subgroups using formalin-fixed paraffin-embedded tissue samples, the TransPORTEC consortium evaluated 116 HREC patients and reported that molecular analysis can discriminate between patients with a favorable and intermediate prognosis (POLE-mutant or microsatellite instability, respectively) and those with unfavorable outcomes (P53-mutant and no specific molecular profile) [69]. Improved selection of patients at risk for recurrence or distant metastasis may help to improve individual tumour-tailored upfront and adjuvant therapy. A risk stratification using integrated clinicopathological and molecular risk factors seems most effective to define risk, determine sensitivity to therapies and find new targets for therapy.

The median age of EC patients at diagnosis is about 65–76 years and they often have comorbidities. For these patients it is important to balance the benefits of adjuvant treatment in terms of progression-free survival benefit, against the costs in terms of toxicity, impaired quality of life and longer treatment time. In a patient preference study done by the ANZGOG group among PORTEC-3 patients the minimum survival benefit to make adjuvant chemotherapy worthwhile was 5% or an extra 1 year for more than 50% of patients [70]. Over 50% of clinicians judged an extra 1 year of survival time or an extra 10% survival benefit sufficient to justify chemotherapy. The reported benefit in progression-free survival found in the recent trials is within this range, although no significant overall survival benefit was found. Therefore, individual patient counseling and shared decision-making remain essential.

5. Five-year view

There is evidence from prospective clinical trials that the addition of adjuvant chemotherapy to radiotherapy improved progression-free survival without a significant overall survival benefit. The benefit of chemotherapy is limited to a subgroup of patients and an important future challenge is to better select the patients who have the most benefit from chemotherapy to reduce over- and under-treatment of women with endometrial cancer.

There is no unequivocal evidence that the known risk factors (histology, LVSI, age) can be used to select patients for the addition of chemotherapy to radiotherapy. Stage III EC (with a higher baseline risk of recurrence) was found to have a significant improvement in failure-free survival in the PORTEC-3 trial. The data from the GOG-249 trial confirmed the efficacy of pelvic radiotherapy for women with stage I-II endometrial cancer with high-risk factors, while 89% of the women had undergone lymphadenectomy. For stage III EC addition of chemotherapy to radiotherapy could be considered to maximize failure-free survival; data on salvage radiotherapy of women who had pelvic relapse in the chemotherapy-alone arm of GOG 258 are eagerly awaited. An improved classification might help selecting the patients who have the greatest benefit of the addition of chemotherapy.

An integrated profile of clinicopathological and molecular risk factors showed an improved risk assessment in intermediate risk EC patients [42,43,71]. This molecular integrated risk profile for women with intermediate risk EC is currently being prospectively tested in the randomized PORTEC-4a trial [49]. In this trial, high-intermediate risk stage I patients are randomized (1:2) to standard adjuvant vaginal brachytherapy or to the experimental arm in which adjuvant treatment is based on the integrated molecular profile. In this arm, patients are divided into three subgroups based on the profile consisting of the TGCA groups POLE mutated, MMR deficient, TP53-mutated and no specific molecular profile; L1CAM expression, LVSI assessment, and beta-

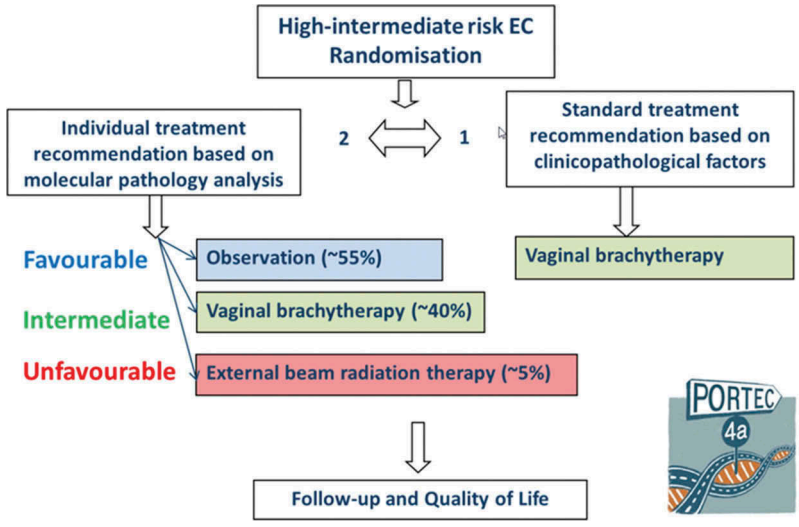

Figure 2. PORTEC-4a trial design.

catenin mutation. The favorable subgroup of otherwise high-intermediate risk EC (approximately 55%) will receive no adjuvant treatment. The intermediate subgroup (40%) will receive vaginal brachytherapy. Patients with an unfavorable profile (5%) will be treated with external beam radiotherapy. The primary end point is vaginal recurrence; secondary end points are pelvic and distant recurrence, overall and recurrence-free survival, quality of life and health care costs (Figure 2).

The TransPORTEC consortium reported in a pilot study that molecular analysis improved risk assessment in HREC as well [69]. To determine the molecular characteristics of a large cohort with HREC patients, translational research will be performed on tumor tissue blocks donated by over 400 PORTEC-3 patients. These molecular subgroups as described by the Cancer Genome Atlas Group will be determined [41], and molecular subclass-specific benefits of combined chemotherapy and radiotherapy will be explored together with assessment of other characteristics and targets such as DNA repair damage, genome scarring, immunological reactivity, and TP53 pathway abnormalities.

Future studies should address the role of the molecular integrated risk classifiers to direct adjuvant treatment of specific subgroups of high-risk endometrial cancer, and to identify molecular alterations sensitive to tailored targeted therapies.

Key issues

- Concurrent chemotherapy and radiotherapy with adjuvant chemotherapy should be considered for women with stage III endometrial cancer to optimize failure-free survival.
- For women with stage I-II endometrial cancer with high-risk features, external beam radiotherapy remains the standard of treatment.
- Higher rates of adverse events and impaired health-related quality of life were reported for patients treated with the combination of chemotherapy and radiotherapy compared to radiotherapy alone.
- Counseling of every individual patient is important to weigh the costs and benefits of adjuvant treatment.
- Translational research is essential to further individualize treatment and determine new effective targeted treatments.

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