Strahlenther Onkol (2018) 194:965–974
https://doi.org/10.1007/s00066-018-1339-6

REVIEW ARTICLE

Evolution of adjuvant treatment in endometrial cancer—no evidence and new questions?

S. Marnitz[1] · C. Köhler[2] · N. Gharbi[1] · S. Kunze[1] · K. Jablonska[1] · J. Herter[1]

Received: 31 May 2018 / Accepted: 12 July 2018 / Published online: 15 August 2018

Abstract

Purpose For endometrial cancer (EC), clinical and pathological risk factors are taken to triage patients and estimate their prognosis. Lymph node involvement (pN+), lymphovascular space involvement (LSVI), grading, age of the patients, and T classification are internationally accepted parameters for treatment decisions.

Materials and methods Studies on adjuvant radiation, chemotherapy, and chemoradiation are discussed against the background of risk stratification and clinical decision-making in early-to-advanced stage endometrial cancer. Recent publications on adjuvant treatment in high-risk disease and its implications for the patients with regard to expected oncologic benefit and treatment-related toxicity are discussed.

Results Surgery is the mainstay of treatment of EC patients. Well-differentiated tumors and early disease (FIGO IA) should be followed up without further treatment. In FIGO I stage without risk factors, VBT remains the standard treatment after surgery. FIGO I, II patients with one or more risk factors (MI ≥ 50%, Grading[G]3, age >60 years, LVSI) benefit from external beam radiotherapy (EBRT) in terms of survival. There are no data of acceptable quality demonstrating that chemotherapy is superior to radiation in locally advanced carcinomas. Therefore, even in locally advanced disease (FIGO III, IV), EBRT remains the standard of care after surgery. EBRT contributes to the very low rate of local relapses and better DFS in these patients and should not be replaced by chemotherapy only. Whether and which subgroups of patients benefit from an additional (concomitant and/or adjuvant) chemotherapy in terms of disease-free survival remains a controversial issue. The recently published PORTEC-3 trial could not create clear evidence. With a high rate of isolated tumors cells and micrometastases in the specimens, the increasing use of unvalidated sentinel concepts in endometrial cancer raises more questions with regard to indications for adjuvant treatment.

Summary and perspectives In the future, integrated genomic characterization of tumors might be helpful for treatment individualization in the adjuvant setting.

Keywords Endometrial cancer · Adjuvant treatment · Radiation · Chemotherapy

Entwicklung der adjuvanten Behandlung beim Endometriumkarzinom – keine Evidenz und neue Fragen?

Zusammenfassung

Hintergrund International akzeptierte klinische und pathologische Risikofaktoren bestimmen die Prognose der Endometriumkarzinom(EC)-Patientinnen und die adjuvanten Therapieentscheidungen.

✉ S. Marnitz, M.D.
simone.marnitz-schulze@uk-koeln.de

[1] Medical Faculty, Department of Radiation Oncology, CyberKnife- and Radiation Therapy, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany

[2] Department of Special Operative and Oncologic Gynaecology, Asklepios-Clinic Hamburg, Hamburg, Germany

Material und Methoden Die vorliegenden Studien zur adjuvanten Therapie werden für die Patientinnen mit lokal begrenzten bis lokal fortgeschrittenen EC kritisch beleuchtet. Die aktuelle Datenlage zur adjuvanten Therapie in der Hochrisikosituation wird differenziert diskutiert, Nutzen und mögliche Risiken für die Patientinnen dargelegt und methodische Schwächen der Daten dargestellt.

Ergebnisse Lokal begrenzte Tumoren ohne Risikofaktoren (FIGO IA), benötigen nach lege artis Operation keine weitere Therapie. Im FIGO-Stadium IAG3,IB ohne weitere Risikofaktoren bleibt die Brachytherapie die adjuvante Therapie der Wahl. Patientinnen mit Befunden FIGO I,II und mindestens einem weiteren Risikofaktor (MI ≥ 50%, G3, Alter >60 Jahre, LVSI) profitieren bezüglich des Überlebens von der EBRT. Für Tumoren der FIGO-Stadien III, IV bleibt die EBRT der postoperative Standard. Die EBRT senkt die lokale Rezidivrate signifikant und verbessert damit das erkrankungsfreie Überleben. Sie kann nicht durch eine alleinige Chemotherapie ersetzt werden. Ob und welche Patienten von einer zusätzlichen (konkomitanten und/oder adjuvanten) Chemotherapie bezüglich des Überlebens profitieren, bleibt auch nach PORTEC-3 kontrovers. Durch die höhere Rate isolierter Tumorzellen und Mikrometastasen nach Anwendung des nicht validierten Sentinelkonzeptes beim EC, ergeben sich neue Fragen bzgl. der Indikationen zur adjuvanten Therapie.

Ausblick In der Zukunft wird die integrierte genomische Charakterisierung der Tumoren helfen, die adjuvante Therapie des EC zu individualisieren.

Schlüsselwörter Endometriumkarzinom · Adjuvante Therapie · Bestrahlung · Chemotherapie

Introduction

Endometrial cancer is the most common gynecological tumor in developed countries, with increasing prevalence [1, 2]. Clinical and pathological risk factors are taken to triage patients and estimate their prognosis. Lymph node involvement (pN+), lymphovascular space involvement (LSVI), grading, age of the patients, and T classification are internationally accepted risk factors for treatment decisions [3–5].

Low-risk disease is defined as myometrial infiltration <50% (FIGO IA) and G1–2. Intermediate-risk patients include those with IAG3 and IB (MI, myometrial infiltration >50%) G1 or G2. According to the GOG-99 study [6], high-intermediate-risk was defined if patients are ≥70 years of age with any one of the risk factors tumor grade 2 or 3, MI > 50%, or LVSI. Patients ≥50 years with any two of the abovementioned risk factors (RF) or patients of any age with all three RF were defined as high-intermediate risk. More advanced stages are defined as high-risk disease.

Clinicians' experience that some of the patients with the low-risk tumors show relapses and rapid progression with distant metastases while most of them have a good prognosis without any adjuvant treatment challenges the conventional classification of type I ("good") for estrogen-dependent tumors and the type II ("bad") tumors [7–9].

Recently, integrated genomic characterization created a new classification with (1) POLE ultra-mutated, (2) microsatellite instability hypermutated, (3) copy number low, (4) and copy number high tumors with distinct risks for progression. This might be a future prospect for better patient selection for adjuvant radiation and/or chemotherapy.

Some aspects of clinical and pathological risk factors need to be discussed.

Lymph node status

Thirty years ago, a randomized trial by the GOG [10] underlined the importance of lymph node involvement for the prognosis of patients. 15 and 16% of patients with clinical stage I, II presented with pelvic and paraaortic metastases, respectively. The latter patients had a poor survival of less than 30% after 5 years. Two decades later, the ASTEC trial and Italian trial [4, 11, 12] could not show any benefit in terms of 5-year overall survival from lymphadenectomy. The use of LNE is declining in stage I patients [13, 14]. In contrast, a Japanese study including mostly patients with intermediate- and high-risk parameters demonstrated a survival benefit of pelvic *and* paraaortic lymphadenectomy compared with only pelvic lymphadenectomy for all subgroups of included patients—low-, intermediate- and high-risk groups [15]. For advanced stages II and III, lymphadenectomy remains a part of surgical treatment. As for cervical cancer, FDG-PET-CT demonstrated a disappointing sensitivity of 65% for detection of pelvic and paraaortic nodes and cannot be recommended for lymph node staging in endometrial cancer [16].

Sentinel node concept in endometrial cancer

Although not validated in randomized studies, there is an increasing use of the sentinel node technique (SLN) [17]. From radiation oncologists' point of view, results of ultrastaging after SLN raise new questions. Plante et al. [18] demonstrated that after sentinel procedure, about 50% of 500 patients had macrometastases, but 13 and 36% showed micrometastases and isolated tumor cells within the lymph nodes, respectively. These 50% of the lymph node findings (micrometastases and isolated tumor cells) have never, or

Table 1 Randomized trials on external beam radiation (EBRT) in FIGO (classification bevor 2009) stage I, II endometrial cancer

Study/author	Year	Patients	Randomization	Local failure (%)	*P*	OS
Norwegian Aalders et al. [19]	1980	FIGO stage I *N* = 540	Surgery + VBT ± EBRT (40 Gy)	1.9 vs. 6.9	<0.05	n.s.
PORTEC 1 Creutzberg et al. [26]	2000	FIGO IB G2/3 ICG1/2 *N* = 715	Surgery ± EBRT	4 vs. 14	<0.05	n.s.
GOG 99 Keys et al. [6]	2004	FIGO IB, IC, II (occult) *N* = 392	Surgery + LAE ± EBRT	3 vs. 12	<0.05	n.s.
ASTEC Group [11]	2009	FIGO I, II intermediate- and high-risk, patients not fit enough for LAE *N* = 905	Surgery ± VBT (center policy) ± EBRT	3 vs. 6	<0.05	n.s.

OS overall survival, *VBT* vaginal brachytherapy, *EBRT* external beam radiation, *OS* overall survival, *N* number of patients, *P* level of significance

at least only accidentally, been seen by conventional histology [19]. The prognostic value of these "new" findings based on ultrastaging and its clinical implication is unclear. Plante and co-authors [18] claim that micrometastases and isolated tumor cells imply a better prognosis. This should be evaluated in a trial randomizing patients with micrometastases and isolated tumor cells to either adjuvant treatment or follow-up.

Grading and stage

For endometrial cancer, most parameters for the treatment decision are given by the pathologists. In the PORTEC-1 study, a substantial shift from grading 2 to grading 1 could be demonstrated after central review of the specimen. Years later again, a central pathology review by expert gynecopathologists changed histological type, grade, or other items in 43% of women with high-risk endometrial cancer [20–22]. This raises the question of how reliable our treatment decisions are on the basis of pathology reports, even outside clinical trials.

Role of adjuvant external beam radiation

The results of four randomized trials are summarized in a Cochrane analysis. In stage I patients, external beam radiation decreases the pelvic as well as the vaginal recurrence rate significantly, without impact on overall survival ([23]; Table 1). The abovementioned studies were underpowered with regard to overall survival (OS), because OS was not the endpoint. However, patients with grade 3 tumors and >50% myometrial invasion achieved an improved survival after EBRT [6, 24, 25], although higher rates and grade of gastrointestinal and genitourinary toxicity were documented after EBRT.

Role of adjuvant brachytherapy

In the PORTEC 2 trial, vaginal brachytherapy versus EBRT were compared in patients with high-intermediate-risk endometrial cancer. EBRT significantly reduced pelvic *and* vaginal relapses, brachytherapy reduced vaginal relapses only. No difference was seen in OS. Given the short treatment time and mild GI toxicity, vaginal brachytherapy has been the standard of care in patients with stage IA G3, IB G1–2 without additional risk factors. Long-term quality of life did not differ between VBT and EBRT ([27, 28]; Table 1).

Some argue against any adjuvant treatment because salvage rates seem to be acceptable in EC patients. Vance et al. [29] evaluated a total of 156 recurrent women with early stage endometrial cancer after hysterectomy with or without adjuvant radiation. The (immediate) adjuvant radiation group had significantly better 5-year disease-specific survival compared with patients after salvage treatment (95% vs 77%, $P < 0.001$) and 5-year OS (79% vs 72%, $P = 0.005$). Salvage treatment caused more toxicity than adjuvant radiation with higher rates of ≥grade 2 GI and ≥grade 2 GU toxicity (23% versus 54% and 3% versus 44%, respectively) in favor of immediate adjuvant treatment.

Role of adjuvant chemotherapy

Against the background of the PORTEC 1, GOG-99, and Norwegian trials which could not demonstrate a survival benefit in patients after radiation, one idea of the new millennium was to replace radiation by chemotherapy. Three randomized trials were performed—the Japanese phase III [30] trial of pelvic radiotherapy versus cisplatin-based chemotherapy in patients with intermediate and high-risk endometrial cancer, the Italian trial evaluation of adjuvant chemotherapy versus radiotherapy in high-risk endometrial carcinoma [31], and the GOG-122 [32] randomized phase III trial which evaluated the whole-abdominal irra-

diation versus doxorubicin and cisplatin chemotherapy in locally advanced endometrial carcinoma.

The Japanese trial [30] included patients with endometrioid adenocarcinoma with deeper than 50% myometrial invasion. Among 385 patients, 193 patients received pelvic radiotherapy with 45–50 Gy with an outdated APPA technique. 192 patients received cyclophosphamide, doxorubicin, and cisplatin every 4 weeks for at least three cycles. The 5-year PFS rates and the 5-year OS rates did not show statistically significant differences between chemotherapy and radiation. Interestingly, after chemotherapy, there were slightly more extrapelvic recurrences. Chemotherapy was more toxic, with ≥4.8% grade 3 toxicity versus 1.6% in the radiation arm. No treatment-related deaths occurred.

For the Italian trial [31], 345 patients in FIGO stage (before 2009) IcG3, IIG3 with myometrial invasion >50%, and FIGO stage III were randomized to either EBRT with 45 Gy or to adjuvant chemotherapy with cisplatin (50 mg/m^2), doxorubicin (45 mg/m^2), and cyclophosphamide (600 mg/m^2) every 28 days for five cycles. Radiotherapy delayed local relapses and chemotherapy delayed distant metastases. Nevertheless, the 3-, 5-, and 7-year progression-free survival rates were 69, 63, and 56% for radiotherapy and 68, 63, and 60% for chemotherapy, respectively (n.s.).

GOG-122 [32] is the only chemotherapy versus radiation study which showed significantly improved results in favor of chemotherapy. It has been one of the most misinterpreted studies in gynecologic oncology. There is a need to highlight the background: The study used an experimental whole-abdomen radiation ($n=202$) versus chemotherapy (doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for seven cycles, followed by one cycle of cisplatin; $n=194$) in women with stage III or IV endometrial carcinoma having a maximum of 2 cm of residual disease after surgery. That implies that the GOG-122 study is not a study for adjuvant, but for locally advanced disease and/or the palliative situation. Neither the used chemotherapy nor the disturbing concept of whole-abdominal radiation with 30 Gy in 20 fractions and a 15 Gy boost to the pelvis and/or paraaortic nodes has been proven for this indication. As a result, adherence to radiation was 84%, and only 63% of the patients received all cycles of chemotherapy. 69 out of 191 patients experienced grade 4 hematologic toxicity during chemotherapy. There were 5 deaths during treatment. In summary, there is no conclusive evidence that chemotherapy should replace radiation in advanced EC patients. Table 2 gives an overview.

Role of adjuvant chemoradiation

As a result of the studies discussed above, it has been shown that chemotherapy is able to reduce (or delay) distant metastases and radiation is effective to decrease local (vaginal and/or pelvic) failures. The consequence was to combine both modalities as done by the NSGO/EORTC [33] and MaNGO-ILIADE-III trials [34]. 534 patients with operated endometrial cancer in FIGO stage I–III with high-risk factors but no residual tumor were randomly allocated to adjuvant radiotherapy with or without sequential chemotherapy. Pelvic radiation was given according to "departmental guidelines" (total dose ≥44 Gy). Optional vaginal brachytherapy had to be decided upon before randomization. Sequential chemotherapy for those patients in the RT + CT arm consisted of four courses of doxorubicin/epirubicin 50 mg/m^2 + cisplatin 50 mg/m^2 every 4 weeks. A later amendment allowed alternative regimens, including paclitaxel 175 mg/m + epirubicin 60 mg/m^2 or doxorubicin 40 mg/m^2 + carboplatin AUC 5 or paclitaxel 175 mg/m^2 + carboplatin AUC 5–6 every 3 weeks (Table 3).

None of the studies showed significant differences in terms of overall survival in favor of combination of radiation and chemotherapy. In the combined analysis of both studies, there was a trend toward improved overall survival (HR 0.69, CI 0.46–1.03; $P=0.07$). Surprisingly, the combined analysis confirmed the positive trend for patients with endometrioid histology only. Patients with serous/clear cell tumors had no benefit at all [34]. For the subgroup of patients with histologically confirmed lymph node metastases (FIGO IIIC), a recently published comparative analysis [37] showed that either radiation or chemoradiation is superior to chemotherapy in terms of distant recurrence-free and overall survival.

Over the past decade, the sequence of chemotherapy and radiation has been a matter of debate. There is no evidence from randomized trials. Alvarez et al. [38] reported on patients with stage III and IV EC who were "optimally" debulked in 83%. The cohort is comparable to those patients included into the GOG-122 trial. Patients benefited from chemoradiation significantly in terms of survival compared to radiation alone or chemotherapy alone. A smaller subset of patients was analyzed for the sequence of treatment. Those patients who received "sandwich" therapy (chemoradiation-chemo) had the longest 3-year OS (91%) and PFS (69%) compared to those treated with either radiotherapy or chemoradiation followed by chemotherapy.

More data were expected impatiently as described for the recently published studies.

PORTEC-3 study

The randomized PORTEC-3 intergroup trial [35] was initiated to investigate the potential benefit of concomitant chemoradiation followed by adjuvant chemotherapy versus pelvic radiotherapy alone for women with high-risk parameters (FIGO stage I grade 3 with deep myometrial invasion

Table 2 Studies on chemotherapy versus radiation in endometrial cancer

Study	Patients	Treatment	Surgery	Radiation	Chemotherapy	Recurrences	PFS (%)	OS (%)
NSGO-EC-9501/ EORTC-55991 1996–2007	*N* = 196 *N* = 186 Patients with surgical stage I, II, IIIA, or IIIC1 With two or more of the risk factors: grade 3, 50% myometrial invasion, or DNA non-diploidy	R: adjuvant XRT vs. XRT plus adjuvant chemotherapy	Lymph node exploration optional; at least TAH-BSO	EBRT ≥44 Gy ± VBT	Before or after EBRT: Until 2004 4 × cisplatin 50 mg/m^2 and doxorubicin 50 mg/m^2 or epirubicin 75 mg/m^2 (AP). After 2004 AP, paclitaxel 175 mg/m^2 or epirubicin 60 mg/m^2 and carboplatin AUC 5 (TEcP), or paclitaxel 175 mg/m^2 and carboplatin AUC 5–6 (TcP)	NA	72 vs. 79 (p<0.05)	82 vs. 84 (p>0.05)
Italian Study 1990–97	*N* = 345 EC FIGO stage IC grade 3, or stage IIA/B grade 3 with ≥50% MI or FIGO stage III	R: EBRT versus CTX	TAH-BSO, and selective pelvic and paraaortic node sampling	EBRT 45–50 Gy	–	–	–	–
JGOG-2033 1994–2000	*N* = 375 Patients <75 years FIGO stage IC-IIIC EC with ≥50% MI	R: EBRT versus CTX	75-years-old and to have undergone an initial surgery, including TAH-BSO with no residual tumor. Pelvic LNE in 96%, paraaortic LNE in 29%	EBRT 45–50 Gy	Cyclophosphamide 333 mg/m^2, doxorubicin 40 mg/m^2, and cisplatin 50 mg/m^2 every 4 weeks for three or more courses	–	84 (EBRT) vs. 82 (CTX) n.s.	85 (EBRT) vs. 87 (CTX) n.s.
GOG-122 -2003	*N* = 396 FIGO stage III or IV endometrial carcinoma of any histology, residual macroscopic tumor ≤2 cm	R: WART versus CTX	(TAH-BSO), surgical staging, tumor resection, and no single site of residual tumor greater than 2 cm. Nodal sampling optional	WART 1.5–30 Gy, boost 15 Gy	Doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) every 3 weeks for seven cycles, followed by one cycle of cisplatin	WART: 13% pelvic recurrence, 16% intraabdominal recurrence, 22% other distant metastases; CTX: 18% pelvic recurrence, 14% abdominal recurrence, 18% other distant metastases	38 (WART) vs. 50 (CTX) p<0.05	42 (WART) vs. 55 (CTX) p>0.05

XRT radiation, *WART* whole abdomnal radiation, *CTX* chemotherapy, *NA* not applicable, *TAH-BSO* total abdominal hysterectomy – bilateral salpingoopherectomy, *EBRT* external beam radiation, *N* number of patients, *vs.* versus, *Gy* Gray

Table 3 Studies on concomitant chemoradiation in endometrial cancer

Study	Patients	Treatment	Surgery	Radiation	Chemotherapy	Recurrences	PFS	OS (%)
PORTEC-3 [35]	*N* = 686 FIGO stage I grade 3 with deep MI and/or LVSI; stage II or III; or serous/clear cell histology	RTX versus RCTX followed by CTX	TAH and BSO LNE left to the discretion of participating centers, while lymph node debulking was recommended in cases of macroscopic LN	EBRT 1.8–48.6 Gy (45 Gy in UK)	2 × cisplatin 50 mg/m^2 in week 1 and 4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 3-week intervals	Vaginal recurrences 2.1% both arms; Pelvic recurrences 1.0% (RCTX) versus 1.5% (RTX); Distant metastases 22.4% (RCTX) versus 28.3% (RTX)	FFS 75 × 5% (RCTX) vs. 68 × 6% (RTX)	81.8% (RCTX) vs. 76.7% (RTX)
RTOG-9708 (feasibility) [36]	G2/3 adenocarcinoma with either OS 50% MI, cervical stromal invasion, or pelvic-confined extra-uterine disease	RCTX followed by CTX	–	EBRT 45 Gy along with cisplatin (50 mg/m^2) d 1, 28. After EBRT VBT	Adjuvant: 4 × cisplatin (50 mg/m^2) + paclitaxel (175 mg/m^2 every 4 weeks)	NA	4-year DFS 81%	4-year OS 85%

XRT radiation, *WART* whole abdomnal radiation, *CTX* chemotherapy, *NA* not applicable, *TAH-BSO* total abdominal hysterectomy – bilateral salpingoopherectomy, *EBRT* external beam radiation, *N* number of patients, *vs.* versus, *Gy* Gray, *LNE* lymphonodectomy, *RCTX* chemo-radiation, *UK* United Kingdom

and/or LVSI, stage II or III, or serous/clear cell histology). Between 2006 and 2013, 103 centers included 686 women who were randomly allocated to radiation (RT) with 48.6 Gy in 1.8 Gy fractions, or chemoradiation (two cycles of cisplatin 50 mg/m^2 in week 1 and 4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 3-week intervals; CRT-Ch). Primary endpoints were overall survival (OS) and failure-free survival (FFS). Median follow-up time was 5 years. Three- and five-year OS for CRT-Ch vs. RT was 84.4% versus 83.9%, and 81.8% versus 76.7%, respectively ($P = 0.183$). Patients with stage III EC had the greatest benefit from the combined treatment: 5-year FFS for stage III was 69.3% for CRT-Ch versus 58.0% for RT ($P = 0.032$), and 5-year OS for stage III was 78.7% versus 69.8% ($P = 0.114$). Also, patients >70 years, with FIGO stage III and/or serous histology had the greater benefit.

As in many other studies on adjuvant treatment in EC, the problem of the PORTEC-3 study is the inappropriate selection of patients. Included were pooled patients in "FIGO stage III" endometrioid carcinoma, which is a very heterogeneous group of patients with, e.g., adnexal involvement (IIIA), infiltration of the parametrium (IIIB), vaginal infiltration, and last but not least, histologically confirmed pelvic (IIIC1) and/or paraaortic lymph node metastases (IIIC2) with considerable differences in prognosis [39, 40]. There is no information available on the subgroups of stage III. Less than 45% in both arms underwent lymphadenectomy (LNE). That means that 55% of all patients with a considerable risk of lymph node metastases could not be exactly staged as IIIC1 or IIIC2, because there were no data on lymph node involvement. This implies a considerable risk for bias. If those patients also underwent LNE, about 30% of them are stage IIIC, which could have led to other results and interpretations. Todo et al. [39] demonstrated the dramatic impact on prognosis of pelvic and/or paraaortic LNE in patients with endometrial cancer. Worst prognosis was associated with pelvic LNE and histologically confirmed lymph node metastases. Favorable prognosis was associated with full (pelvic AND paraaortic) LNE, but only pelvic lymph nodes. Out of consideration for the participating centers and the accrual of patients, LNE was not mandatory in patients with a high risk for lymph node metastases, which is the main weakness of present data.

Negative results in terms of OS for all patients, but positive results for subgroups of the PORTEC-3 study have to be weighed against the treatment-related toxicity: Grade ≥2 events were doubled in the combined arm (94% versus 44% after CRT versus RT). Grade ≥3 events were found in 61% versus 13% (CRT versus RT, ($P < 0.0001$). At 24 months, grade ≥2 sensory neuropathy persisted in 10% versus 1% of the patients (CRT versus RT, $P < 0.0001$) [41]. The chemotherapy in the PORTEC 3 trial could not reduce the high rate of distant metastases (28% with radiation, 22% with chemoradiation). As expected, local control was excellent in both arms.

GOG-258/NRG oncology study

The contrast program to the abovementioned PORTEC-3 study was the randomized phase III study on chemotherapy, only versus chemoradiation. 407 and 406 patients were assigned to either chemoradiation (EBRT $n = 174$; or EBRT ± brachytherapy with concomitant cisplatin 50 mg/m^2 d1, d29, $n = 204$) followed by carboplatin AUC5 plus paclitaxel 175 mg/m^2 q21 × 4 (CRT-Ch) versus chemotherapy only (Ch; carboplatin AUC6 and paclitaxel 175 mg/m^2 q21 × 6) in "optimally" debulked (<2 cm residual tumor) locally advanced endometrial carcinoma [42]. Stage III/IVA endometrioid and FIGO stage I/II serous cancers were eligible. Pelvic ± paraaortic "lymph node sampling," whatever that means, was optional.

Radiation + chemotherapy led to a dramatic reduction of pelvic and vaginal recurrences compared to chemotherapy (19 versus 10%; 7 versus 3%; respectively). Nevertheless, 5-year OS estimation is 70% versus 73% for CRT-Ch versus Ch. No difference in recurrence-free survival could be demonstrated. After 5 years, the rate of distant metastases was slightly lower in the Ch-arm with 21%, versus 27% in the CRT-Ch-arm. Neither the reduction in distant metastases by chemotherapy nor the reduction of local recurrences could be translated into an oncologic benefit of one of the treatment arms. No significant difference in terms of toxicity was reported. Two consequences can be postulated:

- Radiation led to a dramatic reduction of local recurrences and should be not replaced by chemotherapy only.
- Data underlie the need for more aggressive systemic treatment in selected patients. Distant metastases rate is comparable to PORTEC-3, but too high.

Chemotherapy schedule and dose density and endometrial cancer

In the earlier studies, anthracycline-containing regimes were used. Later, paclitaxel plus carboplatin was a commonly used drug combination in endometrial cancer, with response rates of 60–70% in advanced or recurrent endometrial cancer. Neither adjuvant nor concomitant schedules were tested. In contrast to cervical cancer, head and neck cancer, and ovarian cancer, there is no evidence of an optimal treatment regimen nor for dose responsiveness in endometrial cancer in vivo.

According to cervical cancer treatment, cisplatin was used in the concomittant treatment. In RTOG-9708 [36], cisplatin was used for the first time in a simultaneous ($2 \times 50\,mg/m^2$) and concomitant setting ($4 \times 50\,mg/m^2$). Because of the lack of evidence, PORTEC-3 used the simultaneous chemotherapy part from the abovementioned RTOG-9708 and adopted the adjuvant part from cisplatin to carboplatin in a comparable dose. The simultaneous part of the study contained a lower dose density with $100\,mg/m^2$ in five weeks of cisplatin a lower dose density than usually administered ($200\,mg/m^2$ in five weeks). Less cisplatin has been compensated by the adjuvant part with carboplatin AUC5, 4 cycles, every 4 weeks. Nevertheless, focusing on distant metastases, PORTEC-3 presented a disappointing rate of distant metastases of 22% in the combined arm compared with 28% in the radiation only arm.

Unfortunately, two eagerly awaited studies could not clarify the old question on the optimal adjuvant treatment for high-risk endometrial cancer patients. For daily clinical practice, radiation treatment remains the basis of adjuvant treatment in high-risk endometrial cancer. Whether and for whom the combination of simultaneous chemoradiation provides a benefit, remains unclear. It is likely that stage III patients may have a benefit. In this light, the recently published optimistic interpretation of PORTEC-3 seems to be premature [43].

In conclusion, patients with low-risk endometrial cancer are currently treated with hysterectomy and BSO followed by either no further treatment for low-risk (FIGO IA G1,2) or brachytherapy for FIGO IAG3. External beam radiation significantly reduced pelvic and vaginal recurrences in FIGO stage I and II [23, 24, 26, 44].

Although randomized trials were underpowered for overall survival benefit, subgroups of patients with FIGO stage I, II (G3, older age, FIGO ≥IB) might benefit from external beam radiation in terms of survival [6, 45]. Consensus is that patients with locally advanced endometrial cancer, older patients, G3, deep myometrial infiltration are at a higher risk for local recurrence and distant metastases. This implies the use of both radiation and chemotherapy [37, 38, 46]. There are no data on high-risk endometrial cancer demonstrating a superiority of chemotherapy over radiation [34], except GOG-122, which cannot be considered as a contemporary adjuvant study [32]. The combination and schedule of radiation and/or chemotherapy has been a bone of contention for many years. Two studies were initiated to clarify the situation: GOG 258 compared adjuvant chemotherapy versus chemoradiation, PORTEC-3 compared radiation against chemoradiation in patients with high-risk disease. Both studies missed their primary endpoints. PORTEC-3 study showed a better local control in both arms with radiation. Without radiation, 20% of the patients in GOG 258 experienced local failures with chemotherapy only. Patients in both arms did not benefit in terms of distant metastases disease-free survival from potentially toxic chemotherapy.

As a result, radiation remains the standard of care in patients with high-risk disease and FIGO stage III. The conclusion of the recently updated German guideline for endometrial cancer can therefore no longer be considered as an evidence-based recommendation. Nearly 93% of the experts stated that for FIGO stage III, IVA patients, radiation therapy "could" be given additionally to chemotherapy. After the final publication of PORTEC-3, the evidence-based decision should be for adjuvant radiation. Chemotherapy "could" be given additionally, but "should be weighed against the severity and duration of toxicity of combined treatment, especially since overall survival was not significantly improved" with the addition of chemotherapy, as the PORTEC authors stated [35].

Conflict of interest S. Marnitz, C. Köhler, N. Gharbi, S. Kunze, K. Jablonska, and J. Herter declare that they have no competing interests.

References

1. Sheikh MA, Althouse AD, Freese KE, Soisson S, Edwards RP, Welburn S, Sukumvanich P, Comerci J, Kelley J, LaPorte RE, Linkov F (2014) USA Endometrial Cancer Projections to 2030: should we be concerned? Future Oncol 10:2561–2568
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2012) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Int J Cancer 2015(136):E359–386
3. Ballester M, Bendifallah S, Darai E (2017) European guidelines (ESMO-ESGO-ESTRO consensus conference) for the management of endometrial cancer. Bull Cancer 104:1032–1038
4. Panici PB, Basile S, Maneschi F, Lissoni AA, Signorelli M, Scambia G, Angioli R, Tateo S, Mangili G, Katsaros D et al (2008) Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 100:1707–1716
5. Marnitz S, Kohler C (2012) Current therapy of patients with endometrial carcinoma. A critical review. Strahlenther Onkol 188:12–20
6. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, Pearlman A, Mainan MA, Bell JG (2004) Erratum to "A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study" [Gynecol. Oncol. 92 (2004) 744–751]. Gynecol Oncol 94:241–242
7. Levine DA, The Cancer Genome Atlas Research Network (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497:67–73
8. Murali R, Soslow RA, Weigelt B (2014) Classification of endometrial carcinoma: more than two types. Lancet Oncol 15:E268–E278
9. DeLair DF, Burke KA, Selenica P, Lim RS, Scott SN, Middha S, Mohanty AS, Cheng DT, Berger MF, Soslow RA, Weigelt B (2017) The genetic landscape of endometrial clear cell carcinomas. J Pathol. 243(2):230–241. https://doi.org/10.1002/path.4947
10. Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, Thigpen JT (1990) Doxorubicin as an adjuvant following surgery and radiation-therapy in patients with high-risk

endometrial carcinoma, stage-I and occult stage-ii—a gynecologic oncology group-study. Gynecol Oncol 36:166–171
11. ASTEC/EN.5 Study Group, Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, Eisenhauer E, Bacon M, Tu D, Parmar MK, Amos C, Murray C, Qian W (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373(9658):137–146. https://doi.org/10.1016/S0140-6736(08)61767-5
12. Bottke D, Wiegel T, Kreienberg R, Kurzeder C, Sauer G (2007) Stage IB endometrial cancer. Does lymphadenectomy replace adjuvant radiotherapy? Strahlenther Onkol 183:600–604
13. Naumann RW (2012) The role of lymphadenectomy in endometrial cancer: was the ASTEC trial doomed by design and are we destined to repeat that mistake? Gynecol Oncol 126:5–11
14. Creasman WT, Mutch DE, Herzog TJ (2010) ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? Gynecol Oncol 116:293–294
15. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N (2010) Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 375:1165–1172
16. Atri M, Zhang Z, Dehdashti F, Lee SI, Marques H, Ali S, Koh WJ, Mannel RS, DiSilvestro P, King SA et al (2017) Utility of PET/CT to evaluate retroperitoneal lymph node metastasis in high-risk endometrial cancer: results of ACRIN 6671/GOG 0233 trial. Radiology 283:450–459
17. Holloway RW, Abu-Rustum NR, Backes FJ, Boggess JF, Gotlieb WH, Lowery JW, Rossi EC, Tanner EJ, Wolsky RJ (2017) Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol 146:405–415
18. Plante M, Stanleigh J, Renaud MC, Sebastianelli A, Grondin K, Gregoire J (2017) Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: does adjuvant treatment matter? Gynecol Oncol 146:240–246
19. Aalders J, Abeler V, Kolstad P, Onsrud M (1980) Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 56(4):419–427
20. de Boer SM, Wortman BG, Bosse T, Powell ME, Singh N, Hollema H, Wilson G, Chowdhury MN, Mileshkin L, Pyman J, Katsaros D, Carinelli S, Fyles A, McLachlin CM, Haie-Meder C, Duvillard P, Nout RA, Verhoeven-Adema KW, Putter H, Creutzberg CL, Smit VTHBM; for PORTEC Study Group (2017) Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer. Ann Oncol 29(2):424–430. https://doi.org/10.1093/annonc/mdx753
21. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL (2004) Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. Cancer 100:764–772
22. Scholten AN, van Putten WL, Beerman H, Smit VT, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, De Winter KA, Lutgens LC et al (2005) Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 63:834–838
23. Kong A, Johnson N, Kitchener HC, Lawrie TA (2012) Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst 104:1625–1634
24. Creutzberg CL, Nout RA, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW, Lutgens LC, Pras E, van de Poll-Franse LV, van Putten WL, Group PS (2011) Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 81:e631–e638
25. Creutzberg CL (2004) GOG-99: ending the controversy regarding pelvic radiotherapy for endometrial carcinoma? Gynecol Oncol 92:740–743
26. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E et al (2000) Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404–1411
27. Nout RA, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Mens JW, Slot A, Stenfert Kroese MC, van Bunningen BN et al (2009) Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 27:3547–3556
28. Sorbe BG, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B (2012) External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma a prospective, randomized study-quality-of-life analysis. Int J Gynecol Cancer 22:1281–1288
29. Vance S, Burmeister C, Rasool N, Buekers T, Elshaikh MA (2016) Salvage versus adjuvant radiation treatment for women with early-stage endometrial carcinoma: a matched analysis. Int J Gynecol Cancer 26:307–312
30. Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, Kudo R, Japanese Gynecologic Oncology G (2008) Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 108:226–233
31. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, Colombo A, Fossati R (2006) Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer 95:266–271
32. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT, Benda JA (2006) Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 24:36–44
33. Kuoppala T, Maenpaa J, Tomas E, Puistola U, Salmi T, Grenman S, Lehtovirta P, Fors M, Luukkaala T, Sipila P (2008) Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecol Oncol 110:190–195
34. Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, Andersson H, Grenman S, Lundgren C, Rosenberg P et al (2010) Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. Eur J Cancer 46:2422–2431
35. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, Ottevanger PB, Ledermann JA, Khaw P, Colombo A et al (2018) Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 19:295–309
36. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T (2006) Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. Gynecol Oncol 103:155–159
37. Albuquerque K, Folkert M, Mayadev J, Christie A, Liotta MR, Nagel C, Sevak P, Harkenrider MM, Lea JS, Hanna RK, Small WC Jr, Miller DS, Xie XJ, Potkul RK, Elshaikh MA (2017) Adjuvant external radiation impacts outcome of pelvis-limited stage III endometrial carcinoma: a multi-institutional study. Am J Clin Oncol 41(8):792–796. https://doi.org/10.1097/COC.0000000000000371

38. Alvarez Secord A, Havrilesky LJ, Bae-Jump V, Chin J, Calingaert B, Bland A, Rutledge TL, Berchuck A, Clarke-Pearson DL, Gehrig PA (2007) The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. Gynecol Oncol 107:285–291
39. Todo Y, Kato H, Minobe S, Okamoto K, Suzuki Y, Konno Y, Takeda M, Watari H, Kaneuchi M, Sakuragi N (2011) A validation study of the new revised FIGO staging system to estimate prognosis for patients with stage IIIC endometrial cancer. Gynecol Oncol 121:126–130
40. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC (2002) Assessment of prognostic factors in stage IIIA endometrial cancer. Gynecol Oncol 86:38–44
41. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, Ottevanger PB, Ledermann JA, Khaw P, Colombo A et al (2016) Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 17:1114–1126
42. Matei D et al (2017) Randomized phase III study of tumor directed radiation followed by carboplatin and paclitaxel versus carboplatin and paclitaxel in optimally debulked locally advanced endometrial carcinoma. 2017 ASCO Annual Meeting. ASCO. Oral presentation ASCO 2017
43. Krug D, Arians N (2017) Radiochemotherapy improves failure-free survival in stage III endometrial cancer: final results of the PORTEC-3 trial. Strahlenther Onkol 193:1070–1071
44. Sorbe B, Nordstrom B, Maenpaa J, Kuhelj J, Kuhelj D, Okkan S, Delaloye JF, Frankendal B (2009) Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer 19:873–878
45. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B (2012) External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma—a prospective randomized study. Int J Radiat Oncol Biol Phys 82:1249–1255
46. Boothe D, Orton A, Odei B, Stoddard G, Suneja G, Poppe MM, Werner TL, Gaffney DK (2016) Chemoradiation versus chemotherapy or radiation alone in stage III endometrial cancer: patterns of care and impact on overall survival. Gynecol Oncol 141:421–427