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REVIEW ARTICLE

Adjuvant chemotherapy in endometrial cancer

César Gómez-Raposo[1] · María Merino Salvador[1] · Cristina Aguayo Zamora[1] · Enrique Casado Saenz[1]

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Abstract
The role of adjuvant chemotherapy (CT) is controversial in endometrial carcinoma (EC). Surgery alone is usually curative for women who are at a low risk of disease recurrence. The treatment of EC following surgical staging is based on the risk of relapse, which is defined by the cancer stage at diagnosis, histology of the tumor and other prognostic factors such as grade differentiation, the presence of substantial lymphovascular invasion (LVSI), or depth of myometrial invasion (MI). External beam radiotherapy (EBRT) and/or vaginal brachytherapy (VBT) improved local control and are used as adjuvant treatment for early-stage disease. The role of adjuvant CT is controversial in early-stage EC, and there is no uniform approach to the treatment of women with stage III EC or early-staged non-endometrioid EC. Available evidence did not support the indication of adjuvant CT in stage I–II endometroid EC. In those cases at higher risk of relapse, defined as grade 3 tumors with substantial (no focal) LVSI, specifically with deep MI or cervical involvement, could be considered. Adjuvant CT should be administered to stage III EC patients. When RT is indicated (extensive lymph node involvement or deep MI), sequential treatment with RT or "sandwich" regimen may be considered rather than concurrent CRT. The patients with stage IA MI or IB USC may be offered adjuvant CT alone or in combination with VBT, whereas in stage II uterine serous carcinoma patients adding EBRT may be reasonable. Management approach for patients with stage IA without MI USC who underwent a comprehensive surgery remains controversial, and surveillance alone or CT plus VBT is an appropriate option. Early-stage clear-cell carcinoma patients might not benefit for adjuvant CT, but stage III patients might benefit from the combination of CT and EBRT. Stage I–III uterine carcinosarcoma patients might be offered adjuvant CT followed by RT or as a "sandwich" régimen.

Keywords Endometrial cancer · Adjuvant chemotherapy · Chemoradiotherapy · Uterine serous carcinoma · Uterine clear-cell carcinoma · Uterine carcinosarcoma

Introduction

Cancer of the endometrium is the most common gynecologic malignancy in developed countries, with an estimated 63,230 new cases and 11,350 deaths expected in 2018 in the United States [1]. Endometrial carcinoma (EC) is the most common type of uterine cancer. Fortunately, most women with EC have a favorable prognosis, since the majority of patients present with early-stage disease. 5-year survival rates for localized, regional, and metastatic disease are 96, 67, and 17%, respectively [2].

Surgery alone is usually curative for women who are at a low risk of disease recurrence. The treatment of EC following surgical staging is based on the risk of relapse, which is defined by the cancer stage at diagnosis, histology of the tumor, grade differentiation, presence of lymphovascular invasion (LVSI), and depth of myometrial invasion (MI). External beam pelvic radiotherapy (EBRT) and/or vaginal brachytherapy (VBT) improved local control and are used as adjuvant treatment for early-stage disease [3]. The role of adjuvant chemotherapy (CT) is controversial in early-stage EC, and for women with stage III EC or early-staged non-endometrioid EC there is no uniform treatment approach. The purpose of this paper is to provide a complete review of the literature on all aspects related to the potential role of adjuvant CT in EC.

Risk stratification of endometrial cancer

Low risk EC includes women with grade 1 or 2 endometrioid EC that is confined to the endometrium. That group represents about 70% of EC, is associated with an excellent prognosis, and no adjuvant treatment is required [4, 5]

✉ César Gómez-Raposo
cgomezr@salud.madrid.org

[1] Medical Oncology Department, Hospital Universitario Infanta Sofía, Avenida de Europa 34, 28702 San Sebastián de Los Reyes, Madrid, Spain

High-risk EC includes women with stage III EC, regardless of histology or grade, and women with non-endometrioid histologies, such as serous (USC), clear cell (CCC) or carcinosarcomas (UCS).That group includes patients with differential risk of relapse, with 5-year overall survival (OS) between 33 and 67%, mainly among the non-endometrioid EC, as is shown in Table 1 [6].

Intermediate risk EC includes the rest of the patients; women with uterine-limited cancer that invades the myometrium (stage IA or IB) or cervical stromal invasion (stage II). That group represents a heterogeneus group of patients with a medium relapse rate risk of 20–25% [6], including patients with good prognosis (5-year probability of developing metastasis of 3%) and other patients with worse prognosis (5-year probability of metastasis 32%) [7]. Great efforts have been made to indentify that high-intermediate risk (HIR) patients. Large clinical trials of adjuvant EBRT, GOG-99 and PORTEC-1 trials, defined an high-intermediate risk group that have been used in clinical practice for a long time [8, 9]. In the first PORTEC trial, the risk criteria for locoregional relapse were grade 3, age older than 60 years, and outer 50% myometrial invasion. HIR group in GOG-99 was defined based on the prognostic factors including age, tumor grade, myometrial invasion, and the presence of LVSI. However, accuracy of those risk stratification systems is not high [10]. Actually, grade 3 tumors and the presence of substantial LVSI, particularly in presence of deep MI, are considered by international guidelines as the most important risk factors to stratify patients into a high-intermediate risk [4].

Randomized trials of adjuvant chemotherapy in EC

Multiple studies have explored the potential benefit of adjuvant CT in HIR or high-risk EC. However, the design, completion, and interpretation of large randomization trials of adjuvant therapies in EC have been problematic due to the inclusion of varying stages, histologies and types of treatment regimes employed.

NSGO-EORTC and MaNGO-Iliade trial evaluated the role of a platinum-based combination CT after hysterectomy for EC [11]. The administration of adjuvant CT was associated to a trend towards an improvement in OS (75% vs 82%, HR 0.68, $p=0.009$) and a significant improvement in progression-free survival (PFS) (5-year PFS 69% versus 78%; HR 0.63, $p=0.07$). The subset of patients with USC or CCC did not seem to benefit from CT and there was no difference in treatment by stage. That trial is a joint-analysis trial of two different trials and some important caveats must be pointed out. Both trials were independently desingned and there were significant clinical heterogeneity between the trials; the study included a combination of multiple stages with different histological subtypes, used several regimens of a platinum-based CT, and the quality of the surgery performed was low (with only a quarter of patients with pelvic lymphadenectomy).

Maggi et al. reported no differences in OS in 345 patients with stage IC G3, IIA-B G3 with deep MI or stage III endometrioid-type EC treated with cisplatin, doxorubicin, and cyclophosphamide (CAP) compared to EBRT [12]. Susumu et al. confirmed similar results in 385 patients with stage IC–IIIC EC with deeper MI treated with CAP or EBRT, with no differences in PFS or OS [13]. However, among 120 patients in a high-intermediate risk group defined as (1) stage IC in patients over 70 years old or with G3 endometriod EC, or (2) stage II or positive cytology, the CAP group has a significantly higher PFS and a trend towards higher OS. Both trials have relevant limitations, such as the inclusion of mainly patients with advanced disease and the use a CT regimen not currently used.

GOG-122 trial compared whole-abdominal irradiation (WAI) to the combination of cisplatin and doxorubicin in patients with advanced EC [14]. CT significantly improved PFS and OS compared with WAI, but was associated with worse acute toxicity. At 60 months, 50% of the CT patients were predicted to be alive, recurrence free compared with 38% of WAI arm.

PORTEC-3 trial was an open-label randomized trial comparing concomitant EBRT with cisplatin (chemoradiotherapy, CRT) followed by four cycles of carboplatin/paclitaxel CT versus EBRT [15, 16]. That trial involved more than 650 patients with FIGO 2009 stage I, endometrioid-type grade 3 with deep MI or LVSI (or both), endometrioid-type stage II or III, or stage I to III USC or CCC. CRT improved 5-year OS compared to EBRT (81.4% vs 76.1%, HR 0.70, $p=0.0034$) and 5-year PFS (76.5% vs 69.1%, HT 0.70, $p=0.016$). CRT was associated to significantly higher incidences of adverse events [17]. PORTEC-3 trial is characterized by the broad eligibility criteria regarding to tumor stages and histologies. The extent of lymph node removal was left to the discretion of the investigator, and it was performed only in nearly 60% of patients. On subset analysis, the PFS and OS benefit for CRT was greatest for patients with stage III EC and USC of all stages, but did not extend to stage I or II. Excellent local and regional control were

Table 1 5-year survival rates by histology and AJCC stage [6]

Histology	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)
Endometrioid	73.9	85.7	66.9	36.8
Serous	98.4	55.8	33.3	18.3
Clear cell	88.4	67.3	47.8	17.9

reported, and distant metastases were the first type of recurrence (5-year probability 29.1% in the EBRT arm vs 21.4% in the CRT arm). Regarding treatment delivery and CT completion, only 72% of patients completed all four cycles of adjuvant CT. CT was discontinued in 18% of patients; in 9% because of toxicity and 6% for patient decision.

GOG-249 trial was a phase 3 trial comparing EBRT versus VBT followed by three cycles of paclitaxel/carboplatin CT in 601 patients with stage I–II high-risk early-stage EC [18]. That trial included patients with the following characteristics: endometrioid-type stage I with risk factors (grade 2–3, deep MI, LVSI) according to GOG criteria, endometrioid-type stage II, or stage I-II USC or CCC. Pelvic lymphadenectomy was performed in about 90% of patients. At a median follow-up of 53 months, there were no differences in PFS (3-year PFS 83%, HR 0.919, $p=0.31$) between both arms.

Endometrioid-type stage I and II EC

To date, the use of adjuvant CT to treat women diagnosed with stage I or II EC is not supported by available evidence. EBRT or VCB reduces the locoregional recurrence rate (RR), but does not affect OS for certain stage I or II EC.

As previously mentioned, grade tumor, deep MI or substantial LVSI predict for a risk of recurrence and death. Five-year distant metastases rate for patients with grade 3 stage IC endometrial carcinoma included in the PORTEC-1 trial were 31% (compared to 20% for grade 3 stage IB or 3–8% for grade 1–2 stage I patients) [7]. In a pooled analysis of 926 patients included in PORTEC-1 and -2 trials, substantial LVSI and grade 3 were independent prognostic factors [19]. However, in the PORTEC-1 trial there was no central pathology review, and interpretation of LVSI, and even more the classification as "substantial" is a controversial area, so that data are subject of debate.

PORTEC-3 trial included 365 patients with early-stage EC (30% stage, 27% stage II) [15]. With a median follow-up fo 72 months, there were no differences in 5-year OS (83.3% versus 82.0%, $p=0.50$) or RFS (81.3% versus 77.3%, $p=0.58$) in women with stage I–II disease treated with CRT or EBRT alone [16]. In the GOG-249 trial, where 52.9% of the enrolled population had grade 1 or 2 endometrioid tumors, there were no differences in PFS between both arms [18], but pelvic or para-aortic nodal recurrences were more common with VBT and CT versus EBRT (9% vs 4%). Distant metastases were observed in 18% of patients in each arm.

With the available evidence, the benefit of CT for the high-intermediate risk stage I, and high-risk stage I or stage II EC is uncertain. Retrospective series suggest that adjuvant CT for high-intermediate risk patients with EC could reduce the risk of distant metastases, and that sequential adjuvant CT and EBRT might achieve an excellent local and distant control of disease in these settings (Table 2, [20–23]).An analysis of the National Cancer Database (NCDB) showed that addition of adjuvant CT to EBRT in high-risk early-stage EC (defined as FIGO stage IB or II, either USC, CCC or grade 3 endometrioid-type EC) is associated with improved OS [22]. However, observational registry data have several limitations such as quality of histological data or absence of disease-specific survival, and interpretation of those results should be catious.

In our conclusions, available evidence did not support the indication of adjuvant CT in stage I–II endometroid EC, but its use for selected patients could be considered, mainly in those cases at high risk of relapse, considering the presence

Table 2 Outcomes for grade 3 endometrioid-type stage Ib or II EC with adjuvant chemotherapy

Study	Criteria	*N*	Treatment	Outcomes
Reynaers [20]	Grade 3 endometrioid type Stage Ib (MI > 50%) or II	116	Carbo/Pacl × 3 → ± EBRT EBRT/Obs	Distant RR: 10.9% vs 26.2% ** OM: 5.5% vs 31.1%** DRM: 5.4% vs 26.2%**
Garducci [21]	Stage Ib G2–3 Stage II IM > 50% G2–3	192	CT ± RT RT	Distant RR: 2.7% vs 18.4%** 5-year PFS: 86.0% vs 71.3% 5-year OS: 92.3% vs 75.6%
Boothe [22]	Stage Ib–II G3, non-endometrioid	11,726	CT-RT RT	5-year OS: 83.1% vs 79.0%** HR 0.74, CI 95% 0.65–0.84; $p<0.01$
Lester-Coll [23]	Stage II Grade 1–3 endometrioid	3313	RT CT CT-RT	3-year OS: 92% vs 83% vs 93%; $p=0.0004$**

Retrospective series

RR recurrence rate, *PFS* progression-free survival, *OS* overall survival, *OM* overall mortality, *DRM* disease-realted mortality

**Statistically significant

of grade 3 tumors with substantial (no focal) LVSI, specifically with deep MI or cervical involvement.

Endometrioid-type stage III EC

In a 2014 meta-analysis with 620 patients with advanced EC, adjuvant platinum-based CT showed improvement in OS (HR 0.75, CI 95% 0.57–0.99) and PFS (HR 0.74, CI 95% 0.59–0.92) in comparison to EBRT [24].

PORTEC-3 trial included 295 patients with stage III EC [15]. CRT was associated with an 11% absolute improvement of PFS (5-year PFS 69.3% in the CRT group versus 58.0% for the PRT group, $p=0.031$). As previously mentioned, CRT was associated to significantly higher incidences of adverse events.

GOG-258 trial was a randomized phase III trial that compared cisplatin and EBRT followed by carboplatin/paclitaxel with 6 cycles of carboplatin/paclitaxel in 813 patients with optimally debulked, locally advanced EC [25]. No differences in 5-year PFS (59% in CRT arm vs 58% in CT arm, HR 0.90, $p=0.20$) or OS were observed. Significantly, more vaginal and pelvic or para-aortic recurrences were reported in patients treated with CT alone compared with CRT (7% vs 2%, and 20% v 11%, respectively), whereas a nonsignificant trend in distant metasteses was described in patients treated with CRT (27% vs 21%). Regarding tolerability and completition of treatments, only 75% of patients completed treatment of CRT, mainly due to the high toxicity, in comparison with 85% of patients who completed treatment of CT.

JGOG-2043 study was a randomized phase III trial comparing several regimes of CT as adjuvant CT that included a majority of patients in locally advanced EC [26]. The trial compared docetaxel/cisplatin, paclitaxel/carboplatin, and doxorubicin/cisplatin. Five-year PFS and OS were about 75% and 85%, respectively, without significant differences between the three arms of CT.

With these data, the complementarity of CT (in preventing distant failure) and EBRT (in limiting local relapses) is a consistent finding. The benefit of adjuvant EBRT may be related to those patients with higher risk of local recurrence, such as extensive lymph node involvement or deep MI, in concordance with results from GOG-258 trial (72% of patients included were stage IIIC). A NCDB registry study including 8.222 patients with stages III–IVA endometrioid-type EC treated with adjuvant CT showed that addition of EBRT was associated with a modest, but significant 5-year OS benefit compared to adjuvant CT alone, specifically in stage IIIC patients (HR 0.86, $p=0.003$) [27, 28].

But, what is the optimal adjuvant sequence for patients who benefit from combining CT and EBRT? Acceptable approaches include giving EBRT after completion of six cycles of CT, "sandwich" regimen (three cycles of CT before and after EBRT), or concurrent CRT. Increasing evidence supports the use of upfront CT when combined with EBRT. A NCDB cohort study was performed on 5795 endometrioid-type EC stage III–IVA patients who underwent hysterectomy and received CT and/or EBRT [29]. Women treated with EBRT after CT experienced longer 5-year OS than women whto received EBRT before CT (80.1% versus 73.3%, $p<0.001$). Another NCBD analysis, with 1826 stage III EC patients, suggests that a sequential approach with CT followed by EBRT may be more efficacious than CRT (5-year OS 67% versus 62%, respectively, $p=0.006$) [30]. In the absence of definitive prospective data, the results form PORTEC-3, GOG-258, and JGOG-2043 in addition with these retrospective data, could lead to speculate that EBRT should be delivered after completion of CT. "Sandwich" sequencing of adjuvant CT and EBRT has demonstrated to be a safety and efficacy approach in multiple retrospective and prospective studies (Table 3, [31–35]). These series

Table 3 Series of "sandwich" sequencing of adjuvant chemoradiation in locally advanced endometrial carcinoma

Study	Population	Desing	*N*	Treatment	Outcomes
Secord [31]	Stage III (77%) Stage IV (23%)	R	109	CT → RT → CT (41%) RT-CT (17%) CT-RT (42%)	3 year-PFS: 69% vs 47% vs 52%; $p=0.025$ 3-year OS: 88% vs 54% vs 57%; $p=0.011$
Lupe [32]	Stage III (88%) Stage IV (12%) (60% non-endometrioid)	P	43	CT → RT → CT	81% completed treatment 3-year PFS: 53% 3-year OS: 68%
Geller [33]	Stage III (75%) Stage IV (25%)	P	42	Cb/Doc → RT-Cb/Doc	85% completed treatment 3-year PFS: 71% 3-year OS: 90%
Lu [34]	Stage III	R	51	CT → RT → CT (27%) CT-RT (73%)	5-year PFS: 78% vs 85%; $p=079$ 5-year OS: 87% vs 77%; $p=0{,}37$
Onal [35]	Stage IIIC	R	179	CT → RT (53.6%) CT → RT → CT (46.4%)	5-year PFS: 54% vs 65%; $p=0.05$ 5-year OS: 56% vs 74%; $p=0.03$

R retrospective, *P* prospective, *PFS* progression-free survival, *OS* overall survival

suggest that the sandwich approach is feasible, with about an 80–85% of patients that complete the treatment.

In our conclusion, adjuvant CT should be administered to stage III EC patients, and when RT is indicated (extensive lymph node involvement or deep MI), sequential treatment with RT or "sandwich" regimen may be considered a better option than concurrent CRT.

Non-endometrioid EC

An adequate surgical staging is mandatory in USC, CCC, and UCS due to the increased risk of nodal metastases influencing the use of adjuvant treatments. Given the low incidence of these histologies, any recommendation for adjuvant CT remains a challenge. But non-endometrioid EC ischaracterized by their worse prognosis in comparison to endometrioid-type EC; the 5-year OS stratified by histologic type was less than 50% for USC and UCS, 65% for CCC and 91% for endometrioid-type EC [6]. Even more, salvage rate is very high in endometrioid EC because most recurrences are vault, whereas salvage rate for non-endometrioid EC is low due to the high risk of distant recurrences.

Uterine serous carcinoma

The patients with a stage IA polyp- or endometrium- limited (without MI) USC develop up to 10% risk of vaginal cuff recurrences [36–38]. In a series of the Memorial Sloan Kettering Center with 85 women with stage IA without MI invasion USC who underwent comprehensive surgical staging, the 3-year PFS rate was 94.9% and the 3-year OS rate was 98.8%, and adjuvant treatment did not impact outcomes. In contrast, UPSC consortium reported a relapse rate of 11% in 54 patients with stage IA without MI USC who underwent comprehensive surgical staging [39].Surveillance alone as an appropriate approach for patients with stage IA without MI USC remains as a controversial issue.

The patients with stage IA with MI, stage IB or II USC might be treated with adjuvant CT plus VBT or PRT. That recommendation is based on the higher relapse rates and worse survival, because GOG-219 and PORTEC-3 trials failed to demonstrate a benefit for adjuvant CT in early-stage USC or CCC [15, 18], although these studies were not adequately powered for such subset analyses. In a post-hoc, non-preplanified, analysis of the PORTEC-3 trial with 105 patients with stage I to III USC, CRT significantly improved 5-year OS and 5-year SLP in comparison to EBRT (71.4% vs 52.8%, $p=0.037$, and 59.7% vs 47.9%, $p=0.008$, respectively) [16]. However, such subgroup analyses should be interpreted with caution for the relatively small number of patients included, and even more for the joint analysis of stage I–II and stage III patients. Data of adjuvant treatment in early-stage USC from retrospective series suggest an improvement in outcomes for patients with stage I or II USC-treated CT (±EBRT) in comparison to those treated with EBRT or observation(Table 4, [40–44]).The UPSC consortium reported survival outcome of 206 patients with stage I–II UPSC who underwent comprehensive surgical staging [39]. Treatment with adjuvant platinum/taxane CT in stage I patients improved 5-year PFS (81.5%) compared to patients who received RT alone (64.1%) or observation (64.7%) ($p=0.027$) [40]. In patients with stage II USC, 5-year PFS was 86% in CT-treated patients versus 41% in those not receiving CT ($p=0.010$) [45].

Results from the SEER program with 1.838 patients with stage I–IV USC demonstrated that adjuvant EBRT was associated with significant improvement in OS and PFS in patients who receive adjuvant CT [41]. However, in stage I patients, there were no difference in OS (72% vs 72%, $p=0.63$) and (82% vs 81%, $p=0.071$) between CRT and CT groups. Whereas, in stage II patients, CRT was associated with longer OS (72% vs 47%, $p=0.05$) and trend towards longer PFS (PFS 79% vs 59%, $p=0.13$) compared to CT.

In stage III USC, data from PORTEC-3 trial, support the recommendation of adjuvant treatment with CT and EBRT. A NCDB registry study, previously commented, including

Table 4 Series of adjuvant chemotherapy in early-stage uterine serous carcinoma

Studies	UPSC Consortim [38]		Yale New-Haven [39]		Mahdavi et al. [40]		UPSC Consortim [41]		MSKCC [42]	
Stage	IA–IB		IA–IB		I–II		II		IA–IB	II
Arms	Obs ± RT	CT ± RT	Obs ± RT	CT ± RT	Obs ± RT	CT	Obs ± RT	CT ± RT	IVRT + CT	IVRT + CT
N	53	89	43	31	26	13	36	19	34	7
RR (%)	25–30	11**	47	3**	34	7**	50	10**	11.7	42.8
5-year PFS (%)	64.7	81.5**	–	–	65	92**	41	86**	88	71
5-year OS (%)	59.5–70.2	87.6	46	100**	69	100**	–	–	93	71

RR recurrence rate, *PFS* progression-free survival, *OS* overall survival, *Obs* observation, *CT* chemotherapy, *RT* radiotherapy

**Statistically significant

5048 patients with stages III–IVA non-endometrioid-type EC (57.1% USC) showed that addition of EBRT was associated with a significant 5-year OS benefit compared to adjuvant CT alone (57% vs 48%, HR 0.80, $p < 0.00013$) [27].

Clear cell carcinoma

CCC has better prognosis than USC. Indeed, PORTEC-3 trial showed a frequency of recurrence similar between CCC and endometrioid EC [16]. CCC has been underrepresented in large clinical trials (62 patients—about 10%—in PORTEC-3, 88 patients—less than 5%—in GOG-249 trial, 22 patients—nearly 3%—in GOG-258) [14, 18, 25]. There is so limited data for this population that any recommendations are of a low quality, and supported mainly on retrospective series.

Barney reported outcomes on 20 women with stage I CCC treated with VBT with or without platinum-based CT [46]. The 5-year rate of extrapelvic failure was 16%, PFS was 87%, and OS 83%. CT was not statistically associated in improved PFS or OS. The Canadian high-risk endometrial cancer consortium (CHREC) assessed the treatment related outcomes in 91 patients with stage I–IV CCC [47]. The CHREC demonstrated that adjuvant RT was associated with an improvement in OS, but there was no survival advantage for the use of adjuvant CT. A NCDB analysis with 4298 stage I–IV CCC patients suggests that adjuvant CT did not have a meaningful effect on survival [48].

As previously in USC, data from PORTEC-3 trial, support the recommendation of adjuvant treatment with CT and EBRT in patients with stage III CCC. The NCDB registry study with stages III–IVA non-endometrioid-type EC (9.2% CCC) that evaluated the addition of EBRT to CT showed a significant 5-year OS benefit when EBRT is added to CT [27].

In conclusion, adjuvant CT data for CCC are extremely limited and no firm conclusions can be made. Considering the available evidence, in our opinion, adjuvant CT should only be considered for the highest risk patients with CCC, such as stage III patients.

Uterine carcinosarcoma

Adjuvant treatment for UCS remains a challenge because the lack of quality data to support any evidence. In clinical practice, adjuvant management of UCS is similar to treatment algorithm used for USC. Trials in women with stage I and II CS have consistently reported improvement in RR and PFS, but not in OS. GOG-150 trial compared adjuvant CT (three cycles of ifosfamide–cisplatin) to RT in 206 women with UCS (56.6% of them stage III–IV patients) [49]. There were a lower risk of recurrence and death among patients treated with CT, although the differences were not statistically significant. In the phase II GOG-232B trial, 65 women with stage I or II completed resected UCS received three cycles of ifosfamide–cisplatin, and 7-year PFS and OS reported were 54% and 52%, respectively [50]. These limited data demonstrate that ifosfamide-based regimens have activity in the adjuvant setting. GOG-261 study is a non-inferiority phase III trial that evaluated the combination of paclitaxel/carboplatin versus paclitaxel/ifosfamide in chemotherapy-naive patients with stage I–IV, persistent or recurrent carcinosarcoma of the uterus or ovary [51]. In the cohort of UCS (536 patients), the median OS was 37 months in the paclitaxel/carboplatin arm versus 29 months in the paclitaxel/ifosfamide. Paclitaxel/carboplatin showed not to be inferior to paclitaxel/ifosfamide, but superiority could not be proven. The CHREC study demonstrated that adjuvant CT and RT were associated with an improvement in OS in 236 stage I–IV UCS (HR 0.5, $p = 0.01$) [47].There are low quality data to support the administration of adjuvant combined CRT, but, in general, retrospective studies have shown a favorable outcome with sequential RT after CT or "sandwich" regimen ([52–54], Table 5). This is in line with results from the NCB reported in 2017 that showed that adjuvant CRT was associated with a benefit in OS (HR 0.67, 95% IC 0.55–0.81, $p > 0.01$) compared with CT alone in 3538 patients with UCS [55]. In conclusion, early-stage UCS may be offered adjuvant CT (with carboplatin and paclitaxel) followed by RT or as a "sandwich" regimen.

Perspectives

The Cancer Genome Atlas Research Network (TCGA) performed a characterization of EC based on array and sequencing technologies in 373 cases [56]. Exome sequence analysis revealed four groups of tumors. Group 1 (hypermutated), with EEC with somatic inactivating mutations in POLE exonuclease and very high mutation rates, associated with good prognosis (7%). Group 2 and group 3 both showing similar PFS rates. Group 2 included EEC with microsatellite instability, frequently with MLH-1 promoter hypermethylation and high mutation rates (28%). Group 3 tumors included EEC with low copy number alterations (39%). Finally, group 4 (serous-like or copy-number high) showed low mutation rate, frequent TP53 mutations, worse prognosis, and was predominantly composed of most USC, and also some endomtrioid-type EC (26%). Combining POLE mutational analysis with immunohistochemical analysis of p53 and mismatch repair markers (PMS-2 and MSH-6) has been proposed and validated as a surrogate assay that could replicate the TCGA classification [57, 58]. Incorporation of TCGA surrogate classification into pathologic diagnosis may be important to improve assessment of prognosis and clinical management of patients with EC [59, 60]. In this

Table 5 Series of adjuvant chemotherapy in uterous carcinosarcomas

Study	*N*	Treatment	Outcomes
Guttmann et al. [52]	118 Stage I 99 Stage II 19	Obs CT RT CT + RT	Recurrence: HR 0.70; 95% CI 0.54–0.91, $p = 0.01$ OS: HR 0.74; 95% CI 0.58–0.96; $p = 0.02$ Significant benefit to CRT
Dickson et al. [53]	195 Stage I 160 Stage II 35	Obs CT RT CT + RT	Observation: fourfold increased risk of death CRT vs CT PFS: HR 0.43, 95% CI 0.19–0.95; $p = 0.04$ OS: HR 0.94, 95% CI 0.34–2.98, $p = 0.91$
Dickson et al. [53]	108 Stage III	Obs CT RT CT + RT	Observation: 2.5-fold increased risk of death CRT vs CT PFS: HR 0.58, 95% CI 0.27–1.25; $p = 0.17$ OS: HR 0.51, 95% CI 0.22–1.16, $p = 0.1$
Makker et al. [54]	25 Stage I 15 Stage II 5	CT RT	CT vs RT 3-year PFS 35% vs 9% HR 1.74, 95% CI 0.79–3.85; $p = 0164$

Obs observation, *Ifos* Ifosfamide, *DSS* disease-specific survival, *PFS* progression-free survival, *OS* overall survival, *CT* chemotherapy, *RT* radiotherapy, *CRT* chemoradiotherapy

way, the PORTEC-4a trial is a currently on-going phase III trial among women with EC with high-intermediate risk features to investigate the role of an integrated clinicopathological and molecular risk profile to determine if participants should receive no adjuvant therapy, VBT or EBRT based on a favourable, intermediate or unfavourable profile as compared to standard adjuvant VBT.

Grade 3 endometrioid-type EC comprise a mixture of molecular subtypes of EC, rather than a homogeneous group [61]. Identification of POLE mutated may lead to a much better clinical management of these patients, which has been associated with excellent prognosis. Church et al. identified POLE mutations in 6% of women with EC from PORTEC-1 and -2 trial series [62], and Stelloo et al. in PORTEC-3 trial series [63], both confirming association with grade 3 tumors and good prognosis. McConechy et al. confirmed that EC patients with POLE mutations have an improved PFS in a large cohort of 406 women with EC, even in the presence of what are considered high-risk pathologic features, such as grade 3 (62%), deep MI (stage IB; 37%), LVSI (49%) in POLE-mutated tumors [64]. The International Society of Gynecological Pathologis (ISGyP) Endometrial Carcinoma Project propose a multimodality classification system of high grade ECs (grade 3 tumors, but also CCC and USC) that separates the forur genomically-defined groups using POLE mutational analysis and immunohistochemistry for p53 and PMS-2 and MSH-6 [65].

Other relevant biomarkers that may further refine prognosis, particularly in group 3 patients are CTNNB1 mutational status and L1CAM expression. CTNNB1-mutated ECs are associated with significant lower RFS [66], and the expression of L1CAM has been described as a strong predictor of poor outcome in endometrioid-type EC [67]. For these reasons, L1CAM expression and CTNNB1 mutational status have been incorporated into the molecular profiles of PORTEC-4a trial.

The TGCA molecular classification was built upon EC with endometrioid-type EC and USC. Recent studies have applied the same classification to CCC, and observed that all four molecular subtypes identified in the TCGA dataset were represented in CCCs, being group 3 the most frequent [68].UCS has been recently categorized as a high-grade endometrial-type EC. Supervised comparisons with other gynecologic tumors across multiple platforms demonstrated that most UCS tumors share common features with grade 3 serous ovarian, endometrioid-type EC, and USC [69, 70].

High microsatellite instability (MSI-H) status has been identified in nearly of 30% of patients with EC [71]. Data regarding prognosis for patients whose tumors demonstrate MSI-H (or MMR deficiency) are mixed. Some studies have reported better survival outcomes [72–74], whereas other studies have demonstrated worse survival outcomes [75, 76]. The TGCA study demonstrated similar PFS in the two subgroups comprising the majority of EC: the MSI-H ("hypermutated") group and the copy number low or microsatellite stable (MSS) [56]. Thus, the benefit of MMR or MSI testing is limited to the identification of patients with Lynch syndrome, without a clear value as prognostic factor. However, MMR or MSI testing may have an important value as predictive factor to immunotherapy. Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor has a therapeutic efficacy in patients with EC whose tumors are MMR deficient [77]. A subset study with 49 EC patients with MMR deficient treated with pembrolizumab after progression to standard therapy showed a 57.1% overall response rate and a median PFS of 25.7 months. In conjunction with other studies, these data resulted in approval by the US Food and drug Administration (FDA) in May 2017 for thte use of

pembolizumab in patients whose tumors demonstrate MMR deficiency of MSI-H. The role of checkpoint inhibitors in first-line treatment in patients with advanced EC is currently being evaluated as a previous step to study the potential role of immunotherapy in patients with early-stage disease whose tumors are at high risk of recurrence.

Conclusions

Available evidence did not support the indication of adjuvant CT in stage I–II endometroid EC. In those cases at higher risk of relapse, defined as grade 3 tumors with substantial (no focal) LVSI, specifically with deep MI or cervical involvement, could be considered.

Adjuvant CT should be administered to stage III EC patients. When RT is indicated (extensive lymph node involvement or deep MI), sequential treatment with RT or "sandwich" regimen may be considered rather than concurrent CRT.

The patients with stage IA MI or IB USC may be offered adjuvant CT alone or in combination with VBT, whereas in stage II USC patients adding EBRT may be reasonable. Management approach for patients with stage IA without MI USC who underwent a comprehensive surgery remains controversial, and surveillance alone or CT plus VBT are appropriate options.

Early-stage CCC patients might not benefit for adjuvant CT, but stage III patients might benefit from the combination of CT and EBRT.

Stage I–III UCS patients might be offered adjuvant CT followed by RT or as a "sandwich" regimen.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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