

Adjuvant therapy of uterine clear cell carcinoma: a review

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Abstract

Purpose Uterine clear-cell carcinoma (UCCC) is a rare subset of type II endometrial carcinoma with a poor prognosis relative to the most common type of endometrioid carcinoma. Due to its rarity, there has been limited direct evidence of the efficacy of specific adjuvant therapy posthysterectomy in women with UCCC. We present a review of current literature regarding adjuvant therapy of uterine clear cell carcinoma.

Methods We searched for English-language publications through Pubmed using a combination of the following key words: endometrial carcinoma, clear cell carcinoma, recurrence, prognosis, adjuvant therapy, radiation treatment and chemotherapy. Due to the rarity of UCCC, studies were not limited by design or number of patients.

Results There is a paucity of randomized prospective controlled studies focusing on UCCC adjuvant therapy. Findings have largely been derived from retrospective studies of type II endometrial carcinomas or all endometrial cancers as a group. Very few retrospective studies were found to focus on UCCC adjuvant therapy, although certain larger studies did have subset analyses of UCCC patients.

Conclusions For early stage disease, locoregional radiotherapy, especially vaginal brachytherapy, has evidence of efficacy. The therapeutic gain of radiotherapy may be

further improved with the addition of systemic chemotherapy. Evidence for combined radiation therapy with systemic chemotherapy in women with advanced stage UCCC has remained debatable. UCCC-specific studies are needed to determine the best adjuvant therapy for UCCC without the confounding effects of USC and other endometrial cancers.

Keywords Endometrial carcinoma · Clear cell · Adjuvant · Radiation therapy · Chemotherapy · Hysterectomy · Prognosis

Introduction

Endometrial cancer (EC) is one of the most commonly diagnosed malignancies and is currently the most common gynecologic malignancy in the US [1]. The most common histological type in women with endometrial carcinoma (EC) is the endometrioid type or type I. Women with type I EC usually have a favorable prognosis [2–5]. However, about 5 % of patients have uterine clear-cell carcinoma (UCCC), a subset of type II endometrial cancers with a poorer prognosis [4, 6–13]. Five-year survival rates are less than 50 % for stage II and above [4, 6–9]. Traditionally, endometrial cancers have been treated surgically with hysterectomy and bilateral salpingo-oophorectomy, with lymph node dissection [7, 14]. Women with adverse histological types, e.g. UCCC are often required to receive adjuvant therapy posthysterectomy. Adjuvant management options include radiation treatment (RT) alone, chemotherapy alone or a combination of RT and chemotherapy (RTC). However, given its rarity, the optimal adjuvant therapy for UCCC is controversial. Very few studies were devoted entirely to investigate adjuvant

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options solely for patients with UCCC [5, 7, 11, 15–17] and most of the available studies grouped women with UCCC with women with uterine serous carcinoma (USC) or even grouped them as part of women with endometrial carcinoma of all histological subtypes [18–20]. Since there has been limited direct evidence of the efficacy of specific adjuvant therapy posthysterectomy in women with UCCC, we present a review of current literature regarding adjuvant therapy of uterine clear cell carcinoma.

Comprehensive surgical staging is necessary to correctly stage the disease and consequently plan the specific adjuvant therapies necessary. This would include adequate lymph node dissection (pelvic and para-aortic), omentectomy, as well as peritoneal cytology examination. In a retrospective study by Thomas et al. [15], 69 patients with UCCC initially presented with no clinical evidence of extra-uterine disease. However, on surgical assessment 52 % of these patients were upstaged and 20 % revealed lymphatic spread. In fact, the extent of lymphadenectomy has been correlated with survival endpoints [21]. Thus, comprehensive surgical staging is very important for management of UCCC.

While positive peritoneal cytology was excluded from 2009 International Federation of Gynecology and Obstetrics (FIGO) staging for EC, its prognostic significance in women with EC remains controversial. Combining multi-intentional data sets of women with UCCC is essential to study its prognostic impact in women with UCCC. Until then, routine peritoneal cytology examination should be performed in all women with UCCC as part of their surgical staging procedures.

For the purpose of this review, we will address adjuvant therapies in women with FIGO (International Federation of Gynecology and Obstetrics) stages I–II UCCC separately from those with advanced stage.

Early stage disease (FIGO stages I–II)

Observation only

While close observation after hysterectomy with no adjuvant therapy is one common option in women with endometrioid carcinoma of the uterus, the relatively higher recurrence rates [5, 7, 15] with observation in women with UCCC warrant adjuvant therapy. The 2015 National Comprehensive Cancer Network guidelines state that for FIGO stage IA patients with no myometrial invasion, observation after definitive surgery is an option for patients with “no residual disease in the hysterectomy specimen [22]”. While one study reported similar 5-year overall survival (OS) with and without radiation therapy for women with stage IA, there was significant survival benefit

with adjuvant therapy for patients with stage IB and above UCCC [17]. Additionally, women who elected to close observation ended up with tumor recurrence up to 73 % of the time [5, 7, 15]. Given the aggressive nature of UCCC, patients with early stages were eligible to enroll in prospective randomized studies (GOG 249 [23] and PORTEC-3 [24]) examining the optimal adjuvant therapy in women with endometrial carcinoma. There is no adequate data to justify close observation as a recommended adjuvant management option in women with early stage UCCC.

Adjuvant radiation treatment (RT)

Adjuvant radiation therapy has typically been used for treatment of early stage UCCC, the rationale for which has been inferred from outcome data for women with USC and grade III endometrioid carcinoma [2, 5, 9, 13, 15]. Historically, studies have grouped UCCC with USC which has a high propensity for intra-abdominal spread, so whole abdominopelvic irradiation (WAPI) has been suggested for women with UCCC [2, 20, 25–27]. However, in 2003, Murphy et al. [5] reported in a retrospective study on 38 patients with UCCC (58 % had early disease) that while UCCC was associated with a high rate of recurrence and overall poor outcome, a low rate of abdominal recurrence is seen with UCCC, even without whole abdominopelvic irradiation (WAPI). This study suggested that the high abdominal recurrence rate seen in other studies may be a result of not separating UCCC from USC. The authors concluded that routine use of whole abdominal radiotherapy was not warranted. They did, however, find that locoregional radiotherapy to the pelvis [both external beam radiation therapy (EBRT) of 45 in 1.8 Gy daily fractions as well as vaginal brachytherapy at 20 Gy to the mucosal surface] was correlated with decreased recurrence rates. There were no pelvic failures in the 22 patients treated with adjuvant locoregional radiation therapy. In the 16 patients not treated with radiation therapy (five had no adjuvant therapy, eight had chemotherapy alone, and three had hormonal therapy), eight relapsed in the pelvis.

A recent report on 79 patients with early stage type II EC found that 5-year disease-specific survival (DSS) was significantly improved in patients who received radiation therapy (87 %) versus those who did not (58 %, $p = 0.023$) [28]. Likewise, the 5-year recurrence-free survival (RFS) also showed improvement of 84 over 58 % ($p = 0.002$). RT was given as EBRT (median dose of 45 Gy at 1.8–2 Gy per fraction), vaginal brachytherapy (median surface dose of 37.5 Gy in 5–6 fractions), or a combination of both. Twenty-three of the 79 patients had UCCC. Similarly, a large retrospective analysis of 451 UCCC and 882 USC patients from the SEER database found that for stage IB patients, 5-year OS was 66 % with no RT and 76 %

with RT ($p = 0.006$) and was 33.9 % with no RT vs 60.7 % with RT for stage IC ($p = 0.001$) [17].

In the recently closed GOG 249 and PORTEC-3, EBRT rather than WAPI was the recommended radiation treatment volume in the two studies with a radiation dose range from 45 to 48.6 Gy, in 1.8 Gy per fraction [23, 24]. For PORTEC-3, the clinical target volume (CTV) includes the proximal half of the vagina, the parametrial tissues, and regional lymph nodes (internal iliac, external iliac, and distal common iliac, as well as the peri-aortic lymph node region in case of peri-aortic involvement) [24]. Sometimes patients are unable to have adequate surgical staging or lymph node dissection, either by choice or due to surgical complications. Radiation therapy may be of particular necessity for locoregional disease control for these patients.

Vaginal cuff brachytherapy (VCB) has been gaining momentum as a radiation treatment modality for local control of patients with early stage endometrial carcinoma after adequate surgical staging considering its efficacy in reducing vaginal cuff recurrence together with its favorable quality of life profile [29]. For women with UCCC, DuBeshter et al. reported a 96 % local control rate with high-dose rate (HDR) VCB, recommending that vaginal brachytherapy provides adequate local control in stage I USC and UCCC [18]. HDR vaginal brachytherapy was delivered in four fractions of 7.5–10 Gy per fraction to the surface using an Ir192 source to the proximal 5 cm of the vagina. Eight out of the 24 total patients had UCCC and risk of recurrence was similar for USC and UCCC.

Likewise, Fakiris et al. reported the HOG 97-01 study of 19 patients with USC and UCCC (17 patients had early stage disease, three had stage IIIA, and 1 had stage IVB) which found that intraperitoneal ^{32}P and vaginal brachytherapy for USC and UCCC was feasible and well tolerated [30]. Intraperitoneal ^{32}P was delivered within 8 weeks of surgery and VCB was completed within a month of ^{32}P administration with either HDR (21 Gy in 3 fractions to 0.5 cm depth) or low dose rate (65 Gy in 1–2 fractions to the vaginal surface). Of the two patients with UCCC, one (stage IA) had no evidence of disease at 55-month follow-up and one (stage IVB) had intraperitoneal recurrence at 11-month follow-up. A follow-up study was published in 2010 with 23 early stage patients and 4 stage IIIA patients which supported the conclusions of the earlier study, with adjuvant intraperitoneal ^{32}P and vaginal brachytherapy leading to a 3-year OS of 84.2 % [10].

A recent study of 382 patients with FIGO stages I–II EC found no significant difference in survival endpoints between patients treated with vaginal cuff brachytherapy (median dose 37.5 Gy in 3–5 fractions to the vaginal surface) and those treated with pelvic EBRT (44–50.4 in 1.8–2.0 Gy per fraction) [31]. Seven percent of the patients

had UCCC. Again the number of UCCC patients was small to draw any conclusion pertaining to patients with only UCCC. Another study, by Barney et al., found that for stage I UCCC/USC patients (20 % had UCCC), treatment with VCB (21 Gy in 3 fractions) was adequate for 5-year DFS and OS of 87 and 83 % [32].

The efficacy of vaginal brachytherapy specifically on UCCC was examined through a study of 99 patients with UCCC published by Thomas et al. which reported that vaginal brachytherapy (median dose 21 Gy) may be sufficient adjuvant therapy for patients with stage I/II UCCC [15]. Additionally, they found that UCCC may behave less aggressively than USC, a finding that differed from prior reports [18]. Patients with stage I and II UCCC had 5-year survival rates of 79 and 77 %, respectively. Of the 22 patients with early stage UCCC confirmed by systematic lymphadenectomy (half treated with adjuvant RT), only one patient had a vaginal recurrence. Of the presumed early stage UCCC patients with suboptimal lymphadenectomy, there was 33 % recurrence rate, almost all in the pelvis. Thus, the authors concluded that systematic lymphadenectomy is necessary to stage early stage patients and for adequately staged early stage UCCC patients, vaginal brachytherapy is adequate for disease control. This finding was supported by another UCCC-specific study of 80 patients by Varughese et al. which found increased OS with VCB of 21 Gy in 3 fractions or 14 Gy in 2 fractions (140 months with RT vs 50 months without RT, $p = 0.02$) [16].

Contrary to other studies, Abeler et al. found that adjuvant pelvic radiation therapy is not indicated for UCCC because two-third of the 156 surgically treated UCCC patients studied had recurrence outside the pelvis [7]. However, the study included patients with early and advanced-stage disease and lymphadenectomy was not performed in all patients so the findings are difficult to interpret. The high rate of hematological failure in this group likely represented higher stage disease, so these patients may have benefitted from systemic chemotherapy in addition to radiation therapy.

Another school of thought is that chemotherapy may be used to improve outcome with vaginal brachytherapy. The recent GOG 249 study randomized high risk early stage EC patients, including women with UCCC, to pelvic EBRT (45–50.4 Gy) versus vaginal cuff brachytherapy (HDR 6–7 Gy \times 3 or 10–10.5 Gy \times 3 or 6 Gy \times 5) followed by three cycles of paclitaxel and carboplatin [23]. Investigators found that while adjuvant vaginal brachytherapy with chemotherapy was not superior in terms of RFS to pelvic radiation treatment, the hazard ratio for USC/UCCC was 0.608 in favor of vaginal brachytherapy with chemotherapy, although the finding was not statistically significant.

Systemic chemotherapy

Although chemotherapy has usually been indicated for more advanced disease, due to the relative aggressive nature of UCCC, it is often offered to patients with early-stage disease. In fact, GOG 94, a retrospective analysis of patients with clinical stage I/II (not surgically staged) USC or UCCC treated with whole abdominal radiotherapy (30 in 1.5 Gy fractions with a pelvic boost of 19.8 in 1.8 Gy fractions) found that chemotherapy may be beneficial for early stage UCCC [20]. Of the 13 patients with UCCC, 5-year progression-free survival (PFS) was 54 % (vs 38 % for USC), and treatment failures were often in the radiation field. Thus, the study authors concluded that adjuvant chemotherapy is likely necessary for these relatively radioresistant histologies.

Additionally, the NSGO-EC-9501/EORTC-55991 trial of 383 stages I–III EC patients found that the addition of sequential chemotherapy to adjuvant radiation therapy improves PFS in high risk EC patients with no residual tumor (hazard ratio 0.64, $p = 0.04$) [33]. Although there was less effect on the serous and clear cell carcinoma group (hazard ratio 0.83, $p = 0.59$), the relative number of UCCC patients was not reported so the result may be due to USC influence. Another study focusing on 153 patients with UCCC reported that patients with early stage UCCC who received adjuvant chemotherapy (platinum based, consisting of paclitaxel, anthracyclines, cyclophosphamide, or ifosfamide), had better 5-year RFS and OS rates than patients who received only adjuvant radiotherapy [11]. Further studies of patients with UCCC are needed to correlate with these findings.

To more definitively answer whether chemotherapy improves survival endpoints in high risk early stage EC, the GOG 249 and PORTEC-3 studies were designed. GOG 249 found that for USC/UCCC patients, the hazard ratio for RFS was 0.608 in favor of vaginal brachytherapy with chemotherapy over pelvic EBRT, although the result was not statistically significant [23]. PORTEC-3 randomized patients with high risk early stage and locally advanced EC (stage I grade III or stages II–III) to pelvic EBRT alone at 48.6 Gy versus concurrent radiation and cisplatin followed by carboplatin and paclitaxel in order to determine the difference in OS and failure-free survival between the two arms [24]. The study has been closed to accrual but results have not yet been reported.

Based on the very limited data for women with early stage UCCC, it seems that adjuvant multimodality treatment with RTC may provide better outcome by addressing both local and systemic components of disease recurrence. However, this needs to be confirmed with prospective randomized studies. Additionally, for women with adequate surgical staging, vaginal cuff brachytherapy to the

proximal 3–5 cm of the vagina seems as an appropriate adjuvant RT modality.

Advanced-stage disease (stages III–IV)

Chemotherapy

Chemotherapy has been increasingly used as adjuvant therapy for UCCC, especially for advanced stage disease. The rationale has also been inferred from studies based on EC as a whole. Response rates for Taxanes, anthracyclines, and platinum compounds have been reported at around 25–30 % in advanced-stage or recurrent EC for each agent [34–36]. Studies through the Gynecologic Oncology Group then reported that the combination of doxorubicin plus cisplatin (AP) produced response rates of more than 40 % [34, 37]. Data from the GOG 177 prospective study of 273 patients with advanced-stage or recurrent endometrial cancer revealed that adjuvant TAP (paclitaxel, doxorubicin, and cisplatin) therapy improved response rate, PFS, and OS compared to AP (doxorubicin and cisplatin) [38]. These studies were based on patients with all types of EC, so correlation to UCCC must be extrapolated. In GOG 177, only four patients in each study-arm had UCCC.

In 2006, data from GOG 122 was published, indicating that for the 396 patients with stages III and IV endometrial cancer randomized to AP chemotherapy vs whole-abdominal irradiation, chemotherapy with AP improved PFS and OS for most endometrial cancers but had similar efficacy as radiation treatment for UCCC [19]. Subset analysis of the 17 patients with UCCC and 83 patients with USC revealed that while serous histology was associated with shorter PFS and OS, clear cell histology was not, highlighting the possibility that these entities are more different than previously thought. In fact, the hazard ratio for UCCC vs all other cell types was 0.65 for PFS and 0.8 for OS, whereas UPCS was 1.39 and 1.56, respectively. Other studies then focused on the combination of carboplatin and paclitaxel (TC) in order to reduce chemotherapy toxicity. Krivak et al. [39] reported that TC is not clinically inferior to TAP (doxorubicin, cisplatin, and paclitaxel) in terms of PFS and OS and has less toxicity. Most data on chemotherapy has been derived from multicenter studies involving all types of EC, so correlation to UCCC is inferred.

Combined modality therapy (radiation treatment and chemotherapy)

In recent years, there has been increased focus on combined adjuvant therapies (radiation treatment and chemotherapy) in women with advanced stage disease. Lee et al. found that the use of chemotherapy (most commonly

TC) with EBRT (median 45 Gy, with or without 45 Gy to the para-aortic lymph nodes) in patients with high-grade, node-positive endometrial cancer was correlated with improved DFS and OS compared to only radiation therapy [40]. However, subset analysis on chemoradiation treatment for the 12 % of patients with UCCC specifically is not provided. They additionally found that DFS and OS were lower for UCCC than for endometrioid mixed histology, and slightly lower than USC.

Evidence for combined chemoradiation therapy especially for UCCC is unclear. In 2010, the NSOG/EORTC compared pelvic radiation (≥ 44 Gy, according to departmental guidelines) with and without chemotherapy (doxorubicin/epirubicin plus cisplatin) in 540 patients with endometrial cancer (66 patients had UCCC) [33]. The study found improved OS in EC patients treated with adjuvant chemotherapy, but the chemotherapy effect was negligible for the USC/UCCC subgroup, although with wide confidence intervals.

Likewise, Hsu et al. found that there was no significant difference in the PFS and OS of advanced-stage UCCC patients treated with adjuvant platinum-based chemotherapy, radiotherapy or combined chemoradiation therapy [11]. Although there has been much evidence promoting combined chemoradiation therapy in EC in general, there is some evidence to suggest that combined chemoradiation therapy may not be as effective in UCCC. However, the patient population in these studies is small, adversely affecting the generalizability of the findings.

The recent GOG 258 protocol randomized advanced stage EC (stages III–IVA EC including UCCC and USC) to either concurrent cisplatin with volume-directed radiation therapy followed by carboplatin plus paclitaxel or carboplatin and paclitaxel alone to delineate the difference in RFS between the two arms [41]. If there is an adequate population of UCCC patients in this study, the results, especially on subset analysis, will be able to shed more light on the impact of concurrent RTC on the OS of UCCC patients.

The best sequence in terms of radiation and chemotherapy for advanced stage UCCC has not yet been delineated, nor the most suitable chemotherapy agents [42]. Reported sequences for advanced-stage EC include RT then chemotherapy [33, 43], chemotherapy then RT [44], concurrent RT and chemotherapy followed by more chemotherapy [24, 40, 41, 45], and the “sandwich” [46] technique (chemotherapy then RT, followed by more chemotherapy) [42]. Future studies may help us to define the most appropriate sequence for RTC.

Future directions and biomolecular markers

Several biomolecular markers have been correlated with UCCC. UCCC has been found to have PTEN mutations,

leading to frameshift, missense, and nonsense mutations, as well as ARID1A mutations and microsatellite instability [9, 14, 47, 48]. A targeted mutation analysis of 14 cases of morphologically pure UCCC found mutations more frequently involved in endometrial serous carcinoma than endometrioid carcinomas including concurrent TP53 and PPP2RIA. However, in this study, PTEN was not identified, which is more associated with endometrioid ECs [49, 50]. Another study revealed additional mutations in PIK3CA, PIK3R1, KRAS, and NRAS [51]. UCCC is diagnosed histologically but has features that sometimes overlap with endometrioid EC and USC with consequent interobserver variability [49, 51]. Thus, delineation of UCCC-specific biomolecular markers may aid in diagnosis of UCCC leading to more specific research into adjuvant therapy, prognostic significance, as well as provide a focus for targeted treatment.

Paraneoplastic syndrome

There is a distinct association between ovarian clear cell carcinoma and thromboembolic disease, which is generally attributed to the clear cell histology so it is often inferred that UCCC has a similar association [52–54]. In fact, Matsuo et al. found that 32 % in a study of 25 UCCC patients had venous thromboembolism, compared to 8 % for all EC patients (516) in the study [55]. Thus, screening and management of thromboembolism is an important aspect of the adjuvant management of women with UCCC.

Conclusion

There is a paucity of randomized controlled trials focusing on adjuvant therapy for UCCC. Thus, more studies are needed so that the results are not affected by the treatment response of patients with USC. While some studies are difficult to correlate directly to UCCC given its grouping with USC, the general consensus is a need for adjuvant therapy. Several studies report the benefit of adjuvant radiation therapy and chemotherapy on endometrial cancer, even UCCC, but there are discrepancies regarding the efficacy of radiation therapy versus chemotherapy versus RTC. For early stage disease, locoregional radiotherapy, especially brachytherapy is reasonable and may be augmented with the addition of chemotherapy agents [5, 15, 17, 18, 20, 23, 28]. While advanced-stage UCCC may benefit from combined RTC with likely paclitaxel and carboplatin as opposed to chemotherapy or radiation therapy alone, there is some contradictory evidence in this regard [11, 19, 33, 40]. Some studies have hinted at the benefit of chemotherapy for even early-stage UCCC [20, 23], while other studies have found that combined RTC

may not be more efficacious than radiation or chemotherapy alone [11, 33]. However, given the aggressive nature of this disease, until further research determines the most appropriate adjuvant therapy for UCCC, it may be reasonable to discuss the option of combined adjuvant platinum-based chemotherapy with radiation therapy with UCCC patients. Additional UCCC-specific studies are needed to determine the optimal adjuvant therapy for UCCC without the confounding effects of USC and other endometrial cancers.

Compliance with ethical standards

Conflict of interest The authors declare that no actual or potential conflict of interest in relation to this article exists.

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