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A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

Contemporary management of uterine clear cell carcinoma: A Society of Gynecologic Oncology (SGO) review and recommendation☆

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HIGHLIGHTS

- Updated recommendations for the treatment of UCCC are provided.
- Recent results from 3 phase III NRG/GOG trials are incorporated.
- Information about immune therapy in women diagnosed with UCCC is included.
- Recommendations regarding early stage UCCC treatment are modified.

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ABSTRACT

Uterine clear cell cancer (UCCC) is a rare but aggressive disease. Due to its rarity, large, prospective studies focused on UCCC are exceedingly difficult therefore available data are generally from small, retrospective studies. There is also pertinent information from subsection analysis of larger studies that include UCCC and other histotypes. In 2009, the clinical practice committee of the Society of Gynecologic Oncology (SGO) published a review on UCCC aimed at guiding management. Since that publication, there have been developments which are relevant to UCCC, these include availability of data from landmark trials regarding adjuvant therapy, increasing utilization of sentinel lymph node approach and availability of immunotherapy as a treatment option.

This SGO review is updated with all relevant, published information since 2009 considered clinically important for management of UCCC. In addition, it follows the new SGO's style for this type of publication which includes utilization of the question and answer format.

Contents

1. Introduction

Uterine clear cell cancer (UCCC) is uncommon historically accounting for <10% of all endometrial cancers [1–5]. The proportion of endometrial cancer represented by UCCC in general has varied, with a recently published phase III trial reporting that 10% of the study population had UCCC [6]. While it remains possible that the histologic subtype is in fact increasing, an alternative explanation is that the increase in enrollment is driven by the ongoing debate about the optimal treatment of these patients. Clinical experience and subset analysis of large trials suggest that UCCC is generally more aggressive, less sensitive to chemotherapy and associated

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with worse prognosis when compared to other histologic subtypes of endometrial cancer [4,6]. Although the oncology community desires definitive recommendations derived from prospective studies to better guide the management of UCCC, owing to its relative rarity, prospective trials in UCCC alone are nearly impossible to conduct. The majority of the available data to guide the management of women affected by UCCC comes from retrospective studies and subset analysis of large prospective studies. In 2009, the Society of Gynecology Oncology (SGO) published their first review of the management of women with clear cell endometrial cancer [7]. This evidence-based review/management guideline is an update to that original publication and will be presented in the form of answers to important clinical questions.

2. Methodology

Medline was searched between January 1, 1966 and May 30, 2019 for all publications in English where the studied population included women diagnosed with UCCC. To capture all relevant information, multiple phrases were utilized all containing "clear cell" combined variably with uterine, corpus and endometrial. We included retrospective and prospective studies regardless of size, we also extracted information from large prospective studies.

Since this is an update to a previous publication, we focused our attention mostly on the publications that came out in the decade 2009 to 2019. We also incorporated selected information from earlier studies that were not included in the original 2009 publication.

3. Historical data

Completed trials in both radiation and chemotherapy have allowed UCCC patients to be included; however, these women represent a small proportion, traditionally <10% thereby precluding UCCC only trial and robust subset analysis. This has contributed to data being grouped for reporting purposes as high risk and lacks the level of specific detail that can aid a targeted approach to UCCC management. Table 1 depicts clinical trials evaluating various radiotherapy approaches in women with high-risk early stage and/or advanced stage endometrial cancer. In addition, Table 2 depicts results from earlier clinical trials that evaluated various chemotherapeutic regimens in women with advanced stage III or IV and recurrent endometrial cancer that allowed UCCC enrollment. Although presented in aggregrate with other histologic subtypes, the outcomes remain historically important and warrant consideration.

Question 1: How is UCCC different from other endometrial cancers?

Endometrial cancer can be divided into type I estrogen-dependent endometrioid carcinoma (approximately 80–85%) and type II estrogen-independent non-endometrioid carcinoma (approximately 10–21%) [8]. UCCC is the least common of the type II endometrial carcinomas, uterine papillary serous (UPSC) and carcinosarcoma and mixed histology are more common variants [9]. Moreover, patients with UCCC tend to be older and more likely to present with higher stages when compared to those with endometrioid adenocarcinoma [10–12]. McMeekin et al. evaluated the relationship between histology and outcome in patients with advanced and recurrent endometrial cancer who participated in Gynecologic Oncology Group (GOG) first line chemotherapy trials [4]. Although histologic type was not an independent predictor of response, the overall response rate to chemotherapy in patients with UCCC was 32% compared with 44% in both UPSC and endometrioid adenocarcinoma cases. Furthermore, patients with UCCC had a poorer progression free survival (PFS) and overall survival (OS).

UCCC exhibits a heterogenous variety of microscopic patterns namely; solid, papillary, tubular and cystic [13]. The solid pattern consists of clear cells intermixed with eosinophilic cells whereas the papillary, tubular and cystic patterns are made up of hobnail cells with interspersed clear and eosinophilic cells. The presence of glycogen accounts for the clear cytoplasm, while the hobnail appearance results from cancer cells with naked nuclei that have discharged their glycogen and lost most of their cytoplasm. All the patterns are associated with marked nuclear atypia and high mitotic activity. Immunohistochemistry profiles of the high-risk endometrial cancers often overlap. In a series of 17 cases of clear cell histology from 3 gynecologic subsites including endometrium, cytokeratin 7 (CK7), low molecular weight cytokeratin (CAM5.2), high molecular weight cytokeratin (34βE12), carcinoembryonic antigen (CEA), Leu-M1, vimentin, BCL-2, p53, and CA 125 were all positive. On the other hand, CK 20 and progesterone receptor (PR) were negative with estrogen receptor (ER) and HER-2/neu both having variable positivity [14]. Compared to endometrioid histology, E-cadherin which are cell surface glycoproteins that mediate cell-to-cell adhesion is significantly less expressed [15–17].

Using cDNA array technology Zorn et al. studied 80 cancer cases from uterus, ovary, kidney and 7 normal epithelial brushings. Serous and endometrioid cancers showed gene expression patterns reflecting their organ of origin whereas clear cell cancers showed remarkably similar gene expression regardless of their organ of origin [18]. In one recent study somatic mutation profiles of UCCC were studied by whole exome and targeted sequencing. Among the 63 cases of UCCC evaluated, the following frequent somatic mutations were identified: *TP53* (39%), *PIK3CA* (23.8%), *PIK3R1* (15.9%), *ARID1A* (15.9%), *PP2R1A* (15.9%), *SPOP* (14.3%), *TAF1* (9.5%) and MSI (11.3%). Based on MSI and patterns of gene mutations, the authors concluded that subsets of UCCC molecularly resemble UPSC or endometrioid adenocarcinoma and *TAF1* was implicated as a candidate driver gene in a subset of UCCC [19]. Moreover, the presence of as little as 10% of UCCC in a mixed endometrial cancer histologic presentation appears to confer a similar risk of recurrence and survival when compared to pure UCCC [20]. In conclusion, while aspects of UCCC's clinical behavior, histology and genetics overlap with other high grade cancer histotypes, in

Table 1
Summary of prospective studies of post-operative radiation in endometrial cancer including clear cell histology.

Author, year	Surgical staging	Stage	ARMS	RAD	PFS (3 or 5 years)	*P*	OS (3 or 5 years)	*P* value
Creutzberg et al., 2000 (PORTEC)	No	I	PXRT	PXRT	96%	<0.001	81%	NS
			NFT	None	86%		85%	
Sutton et al., 2005 (GOG-94)	Yes	III & IV	Single	WAPI	27%	NA	35%	NA
Sutton et al., 2006 (GOG-94)	Yes	I & II	Single	WAPI	38%	NA	NA	NA
(PORTEC-3)	No	I, II & III	PXRT	PXRT	75.5%	0.022	81.8%	NS
			PXRT + CT	PXRT & CT	68.6%		76.7%	

PFS = progression free survival, OS = overall survival, p = measure of significant, PXRT = pelvic radiotherapy, NFT = no further treatment, VBT = vaginal brachytherapy, CT = chemotherapy, WAPI = whole abdomen and pelvic radiotherapy, N/A = not applicable and NS = not significant.

Table 2
Results of phase III trials of intravenous chemotherapy in endometrial cancer including clear cell histology.

Author, year	ARMS (chemotherapy)	OR (%)	*P*	PFS (m)	*P*	OS (m)	*P*
Thigpen et al., 2004 (GOG-107)	A,60 mg/m^2	25	0.004	3.8	0.14	9	NS
	A,60 mg/m^2 + C,50 mg/m^2	42		5.7		9.2	
Fleming et al., 2004 (GOG-163)	A,60 mg/m^2 + C,50 mg/m^2	40	NS	7.2	NS	12.6	NS
	A,50 mg/m^2 + P,150 mg/m^2 (24h) + F	43		6		13.6	
Fleming et al., 2004 (GOG-177)	A,60 mg/m^2 + C,50 mg/m^2	34	<0.01	5.3	<0.01	12.3	0.037
	A,45 mg/m^2+ C,50 mg/m^2 (D1) + P,160 mg/m^2 (D2) + F	57		8.3		15.3	
Gallion et al., 2003 (GOG-139)	ST:A,60 mg/m^2 + C,60 mg/m^2	46	NS	6.5	NS	11.2	NS
	CT:A,60 mg/m^2 + C,60 mg/m^2	49		5.9		13.2	

A = adriamycin, C=cisplatinum, CA = carboplatin, P=paclitaxel, F=filgastrim, p = measure of significance, OR = overall response rate, PFS=progression free survival, OS=overall survival, m = months, NS=not significant, D = day, ST = standard timed, CT = circadian timed.

totality, UCCC is unique and different from any other type of endometrial cancer.

Question 2: Do all patients with a pre-operative biopsy of UCCC warrant specific pre-operative assessment such as imaging and tumor markers?

In addition to the general pre-operative work-up, the pre-operative assessment for cancer surgery is best driven by the known clinical profile of the cancer. For UCCC, the evaluation should consider its propensity for extra-uterine spread. If clinical symptoms or examination suggest pelvic side wall involvement due to pain or lack of mobility, a contrasted pelvic MRI may be informative prior to surgery. Diffusion weighted (DW) MRI has improved endometrial cancer evaluation with an increase in the detection of local extension into the cervix and other extra-uterine spread. Specifically, the sensitivity, specificity, positive predictive and negative predictive values for DW MRI images for assessing myometrial invasion are 84.6%, 70.6%, 52.4%, and 92.3% respectively. In addition, this modality is helpful in patients who have contraindications to dye [21–24].

As with other endometrial histologies, preoperative evaluation of gross and/distant extrauterine spread of UCCC can be accurately assessed by imaging including CT of the chest/abdomen and pelvis or PET/CT. Although endometrial cancer shows intense FDG uptake which can be of prognostic significance when PET/CT is utilized, its utility in early endometrial cancer is restricted due to spatial resolution and physiological uptake [25,26]. The sensitivity, specificity and accuracy of PET/CT in detection of lymph node metastases based on increase tracer uptake by the lymph node was reported as 53%, 99%, 98%, respectively and appears superior to MRI [27–29]. For most patients undergoing initial surgery for UCCC, staging contrasted CT scan is sufficient and less expensive than PET/CT.

Advanced stage UCCC can be associated with elevated pre-operative serum CA-125 levels, which may be of prognostic significance. Several studies found correlation between elevated CA-125 and reduced OS [30–32]. Pre-operative serum CA-125 therefore may compliment imaging in guiding surgical approach and potentially adjuvant therapy considerations, including possible use as the tumor marker for monitoring response to therapy.

In conclusion, in view of the aggressive behavior of UCCC and its parttern of spread, pre-operative 3-dimensional imaging and serum tumor markers can be helpful in initial management planning.

Question 3: Do patients with biopsy proven UCCC warrant extended surgical staging to include omental assessment?

Approximately 40–50% of patients with UCCC clinically confined to the uterus at diagnosis have extrauterine spread of disease if surgically staged [33,34]. Although UCCC is more likely to present with extrauterine spread compared to lower grade endometrioid histology, in fully staged patients with confirmed early stage disease, prognosis can be favorable [35].

Overall, the prevalence of lymph node metastasis in UCCC is 25% [36]. The risks of pelvic and para-aortic lymph node involvement in patients with UCCC are 20–26% and 12–15% compared to those with low grade endometrioid histology where the risks are 7–15% and 4–10%, respectively [9,37]. Thomas et al. suggested that omentectomy may not be a necessary component of UCCC staging due to the absence of surgical upstaging based solely on omentectectomy in their study [34]. However, other studies have questioned that finding indicating that the omentum is a common site of extrauterine spread of UCCC. In a series of 53 UCCC cases, 9 of the 12 patients with extra-uterine disease had omental involvement [38]. Moreover, Saygili et al. reported on 97 patients with clinical stage 1 cancer who were subsequently fully staged, including omentectomy, with a 6% rate of omental involvement. Although UCCC represented 5% of the cases in this series, it accounted for 33% of the omental metastases [39]. A more recent study reported a 10% rate of omental metastases by UCCC [40]. Surgical approach (minimally invasive versus laparotomy) can be influenced by pre-operative investigation findings, in suitable candidates, minimally invasive surgical approaches for initial management appear to be reasonable without any detrimental impact on outcomes [41–43]. Although available data is conflicting, extended surgical staging including omentectomy is encouraged as it will allow for accurate prognostication and appropriate adjuvant therapy determination.

Question 4: Is sentinel lymph node dissection (SLND) a reasonable consideration in UCCC or should comprehensive lymphadenectomy be considered the standard of care for UCCC?

The complications and morbidities of systematic pelvic and para-aortic lymphadenectomy are well known. In endometrial cancer, these complications include lymphedema, neuro-sensory disorders, ileus, need for blood transfusion, venous and arterial thrombo-embolism [44]. The incidence and severity of these complications can be reduced or eliminated by an appropriate utilization of sentinel lymph node approach [45]. The question remains as to whether SLND is safe to use in UCCC and other high-grade endometrial cancer histologies. The FIRES trial prospectively evaluated the accuracy of SLND in detecting endometrial cancer metastasis in a cohort of 385 patients. Although, there were only 6 cases of UCCC in this cohort, the sensitivity of the SLN approach was 97.2% with a negative predictive value of 99.7% [46]. Others have evaluated the sensitivity of SLN in high-grade endometrial cancer histologies including UCCC and most of them have suggested the approach is safe. The sensitivity, negative predictive value and false negative rates from these studies are 90–100%, 96–100% and 0–10% respectively [47–49]. It therefore appears reasonable to consider SLN approach as safe for the management of UCCC in the absence of clinically or radiologically detectable adenopathy. If a SLN approach is utilized, utilization of a standard algorithm or

approach similar to that recommended by the National Comprehensive Cancer Network (NCCN) should be utilized [50]. What remains less clear is the preferred evaluation approach for the para-aortic lymph nodes. Accordingly, investigates that utilize a SLN approach should consider the potential pros and cons of para-aortic lymphadenectomy as a potential adjunct to SLN for women without obvious extrauterine spread of their UCCC.

Question 5: Is adjuvant chemotherapy beneficial in early stage (stages I & II) UCCC?

Adjuvant chemotherapy is commonly given to women treated for UCCC even when diagnosed in early stages (stages I–II). Considering the potential side effects of chemotherapy, the role and impact of adjuvant chemotherapy on outcomes in the early stages of UCCC is worth exploring. A few studies have reported UCCC specific data. In one study of 22 UCCC patients undergoing optimal staging surgery for stages I–II disease, half of the patients were observed and the other half received adjuvant therapy. After 44 months of follow up, there were no differences in recurrence rate or death between the two groups [34]. Zhang et al. reported on 97 cases of stage I–II disease consisting of 15% UCCC and 85% UPSC that underwent comprehensive surgical staging which included lymph node assessment in 86–94% and omentectomy in 82–88% of cases. Post-operative adjuvant radiotherapy was similar between the two groups, while adjuvant platinum-based chemotherapy was more common in UPSC compared to UCCC (67% vs. 35%, $p = 0.02$). At five-years, UCCC cases had similar disease-free, disease-specific and OS with a similar pattern of recurrence between the two groups. This and other data suggest a potential lack of benefit from adjuvant chemotherapy in adequately staged cases of UCCC with stages I and II disease [51]. Importantly, the most recent randomized controlled trial from the GOG limited to early stage disease, GOG 249, included only 28 patients with UCCC which precluded definitive conclusions on the role of chemotherapy in these patients [52]. Given the high propensity for recurrence and the difficulties associated with recurrent disease treatment, adjuvant chemotherapy remains a reasonable option in early stage UCCC. Alternatively, in appropriately surgically staged patients with stage IA and IB disease, selective omission of chemotherapy may be considered after appropriate counselling.

Question 6: Is adjuvant radiotherapy beneficial in early stage UCCC?

Similar to adjuvant chemotherapy, there are no prospective studies of adjuvant radiotherapy limited to UCCC alone. Although, database studies did not show any benefit for adjuvant pelvic radiotherapy in women with early stage UCCC [53], multiple retrospective studies have evaluated the impact of adjuvant brachytherapy in UCCC, with most suggesting a reduction of recurrence risk [35,54,55]. In the adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3) trial, 62 women with UCCC were randomized to radiotherapy or radiotherapy with chemotherapy (chemo-radiotherapy). PORTEC-3 patients were randomly assigned in a 1:1 fashion to 48.6 Gy of pelvic radiation therapy versus the same dose of radiation therapy administered in conjunction with two cycles of cisplatin 50 mg/m^2 during week 1 and 4, followed by four cycles of paclitaxel 175 mg/m^2 and carboplatin AUC 5 and OS was similar in both groups. For patients with stages I and II disease including UCCC, 5-year failure-free survival was 80·8% (74·1–86·0) in the chemoradiotherapy group versus 76·6% (69·5–82·2) in the radiotherapy group (0·85, 0·54–1·33; $p = 0·47$). Thus, the addition of chemotherapy did not appear to improve treatment outcome in enrolled patients with early stage disease [6]. The National Cancer Database (NCDB) was used to evaluate adjuvant brachytherapy and chemotherapy in 1246 UCCC patients with disease confined to the endometrium (stage IA). On subset analysis for each high-risk histology, the benefit of brachytherapy was maintained, with UCCC showing 3-year OS rates of 90.5% with brachytherapy vs 83.9% without brachytherapy ($p = 0.006$). Multivariate analysis confirmed the benefit of adjuvant brachytherapy but failed to show benefit for adjuvant chemotherapy in patients with stage IA UCCC [56]. In women diagnosed with FIGO stages I–II UCCC, adjuvant radiotherapy might improve treatment outcome and is recommended for consideration.

Question 7: Is adjuvant chemotherapy beneficial in advanced stage (stages III & IV) UCCC?

Unlike stage I and II UCCC, practice patterns are more similar regarding the utilization of adjuvant chemotherapy in women diagnosed with stage III and IV disease. Although a recent NCDB study suggested that adjuvant chemotherapy, when controlling for stage among other variables, did not have a meaningful effect on the survival of patients with UCCC [57], adjuvant chemotherapy is generally offered to patients with advanced stage endometrial cancers making it difficult to compare the outcomes of adjuvant chemotherapy versus no further treatment. It is important to note however that prospective trials dedicated to chemotherapy evaluation in this specific group are lacking.

Several GOG phase III chemotherapy trials included UCCC with other histologies in patients with stage III, IV and recurrent endometrial cancer [58–61]. When summarized, these trials reported an overall response rate of 25% for single agent doxorubicin, 34–49% for doxorubicin/cisplatin (AC) or doxorubicin/paclitaxel doublet and 57% for the doxorubicin, paclitaxel and cisplatin (TAP) triplet. While TAP had a statistically significant improvement in OS when compared to AC, there was significantly more grade 3 neurologic toxicity in patients receiving TAP, 27% vs. 4%. A GOG ancillary study investigated the relationship between histology and outcomes in advanced and recurrent endometrial cancer patients. Only 3.7% had UCCC and the overall response rate was 32% for UCCC compared to 44% for the other histologies [4]. GOG 209 compared the TAP regimen with carboplatin and paclitaxel in a randomized phase III non-inferiority trial which enrolled patients with advanced and recurrent endometrial cancer including 46 patients with UCCC. This trial has been presented but not yet published. Presented data indicated that the carboplatin plus paclitaxel combination was not inferior to the TAP regimen in efficacy but was less toxic. As a result, the carboplatin plus paclitaxel combination has become widely incorporated into clinical practice and became the control arm of subsequent clinical trials [62]. Most recently, GOG 258 evaluated the role of the addition of cisplatin on Day 1 and 29 to volume directed radiation therapy with or without vaginal cuff brachytherapy followed by an abbreviated course of four cycles of paclitaxel 175 mg/m^2 and carboplatin AUC 6 every three weeks versus a full course of chemotherapy consisting of six cycles at the same doses. Similar to GOG 249, although eligible for trial enrollment, UCCC was again vastly underrepresented with only 22 of 736 (3%) eligible patients enrolled and treated [63]. Accordingly, the exact role of chemotherapy for women with advanced stage UCCC remains debated. However, GOG 258 did not include an observation arm and a prospective trial including observation alone versus active chemotherapy in UCCC is neither feasible nor ethical, we recommend adjuvant chemotherapy for women diagnosed with advanced stage UCCC.

Question 8: What is the prognosis and what are the risk factors for UCCC?

Although controversial even in patients with early stage disease, the risk of recurrence is thought to be higher and thus potentially justifying post-operative adjuvant therapy. Currently NCCN recommends adjuvant therapy, including the options of chemotherapy with or without pelvic radiation as well as vaginal cuff brachytherapy for all patients with stage IB or higher with observation being limited to those with stage IA tumors without myometrial invasion [41].

Perhaps the most comprehensive assessment of baseline risk factors and surgical staging implications for endometrial cancer is GOG 210. GOG 210 was a surgical and pathologic study that prospectively enrolled women with biopsy proven endometrial cancer, of all histologies, who were deemed candidates for hysterectomy with bilateral salpingo-oophorectomy as well as pelvic and para-aortic lymphadenectomy [9]. In addition to pathologic specimens from surgery, both urine and serum were collected. Initially, the trial was unrestricted and allowed all histologic subtypes to enroll although for the last portion of the trial, restrictive criteria were applied in order to increase enrollment of high-grade endometrial cancers including UCCC. Five thousand, eight hundred and sixty six evaluable women with endometrial cancer were accrued, including 311 (5.3%) women with UCCC. The initial accrual on the trial included 129 (3.5%) cases of UCCC from 3715 women entered during the unrestricted portion of the study and 182 (8.5%) of the 2151 cases from the restrictive portion. Pathologically, women with UCCC had outer one-half and-or serosal involvement present in 33% of the collected specimens, with positive pelvic nodal rates and para-aortic nodal rates of 20.1% (55/274) and 12.4% (34/274) respectively. These findings were fairly similar for those with UPSC, carcinosarcoma and high-grade endometrioid endometrial adenocarcinoma, and again provide clear prospective data regarding the importance of comprehensive surgical assessment [7,41].

Additional studies have attempted to elucidate other potential risk factors which might impact prognosis. A large clinicopathologic review of 1023 confirmed endometrial cancers from 1953 to 1976 was conducted [10]. They included 56 (5.5%) UCCC cases, the authors confirmed that early stage disease was directly correlated with survival, with all survivors having stage I disease at the time of diagnosis, and that age and race impacted outcomes. Specifically, the median age at diagnosis was 67, approximately 7 years older than other endometrial histologies, with the five-year OS being only 20.9% for women diagnosed over the age of 60. Although survival was rather descriptive as opposed to more recent studies utilizing more advanced statistical tests, five-year OS in black women was reported to be 12.5% versus 39.1% for white women. There was no statistical comparisons of this finding.

In a more modern review of potential risk factors in UCCC, Rauh-Hain and colleagues performed a large retrospective cohort study utilizing the Surveillance, Epidemiology, and End Results (SEER) data for patients with ovarian (OCCC) or UCCC [64]. The study objective was to evaluate outcomes based on baseline demographics as well as treatment. 5421 women with clear cell malignancies from 1988 to 2010 meeting eligibility criteria were identified including 1790 (33%) patients with UCCC. The mean age at diagnosis was 67.7 years compared to 56 in OCCC, and women with UCCC were five times more likely to be African American than those women with OCCC. For the entire population, advanced age, African American race, lack of surgery, Central SEER registry location, absence of nodal assessment and advanced stage were all predictive of a greater risk of cancer related mortality.

While descriptive, prospective as well as retrospective outcome data are important to inform clinicians and patients about the potential impact of having a diagnosis of UCCC, ultimately prospective clinical trial data is needed to help elucidate ideal therapy recommendations. To that end, a series of clinical trials, including GOG 99 [65], GOG 249 [66], and the PORTEC series [67,68] were performed in order to define a group of patients at increased risk of recurrence and to evaluate different types of adjuvant therapy and its impact on outcomes. GOG 99 identified risk factors for recurrence such as lymphovascular space invasion, grade 2 or 3 tumors and deep myometrial invasion and age, although UCCC were excluded from the trial, its findings informed the design of subsequent trials which allowed the inclusion of both UCCC as well as UPSC. Not surprisingly, although GOG 249 allowed these high risk histologic subtypes, only 28 (5%) patients with UCCC were enrolled [66]. The experimental arm of vaginal cuff brachytherapy and adjuvant chemotherapy, consisting of three cycles of paclitaxel and carboplatin, was not associated with an improvement in either recurrence free or OS as compared to WPRT. The low proportion of UCCC patients in GOG 249 precludes any specific conclusions for individuals with this histology.

While risk factors which predict higher recurrence have been identified and used to stratify adjuvant therapy, a positive impact of such therapy on OS has been elusive as clinical trials have noted only an improved PFS without an impact on OS. Also, while depth of myometrial invasion, tumor grade and the presence of lymphovascular space invasion were identified as reproducible risk factors that predict a higher risk of recurrence for endometrioid adenocarcinoma, insight into these factors and others in UCCC is lacking. At present, clear cell histology is considered a high-grade histology, and thus using prior criteria, all patients with UCCC would have at least one pathologic risk factor regardless of tumor size or depth of myometrial invasion. In spite of this designation, it remains challenging to further subdivide similar stage UCCC patients into lower or higher risk of recurrence for the purpose of treatment planning. Most recently an extensive review of genomic features in endometrial cancer, The Cancer Genome Atlas (TCGA) study, evaluated 373 endometrial cancer specimens in an attempt to determine if genomic features could be identified that could predict outcomes in these patients [69]. Unfortunately, the series was primarily endometrioid (82%) and serous tumors (14%) with only 13 tumors being classified as mixed histology tumors without mention of clear cell histology. Perhaps, forthcoming molecular information from GOG 210 will allow the future stratification of UCCC. In conclusion, compared to other endometrial cancer histotypes, women diagnosed with UCCC are more likely to be older, of African Amerian ethnicity and UCCC diagnosis is associated with worse prognosis.

Question 9: What is the role of adjuvant radiotherapy in advanced Stage UCCC?

While the ideal adjuvant radiation for patients with endometrioid endometrial continues to be debated, clinical trials have evaluated various radiation approaches in women with all stages of endometrial cancer. Modalities evaluated include: whole abdominal radiation, whole pelvic radiation therapy either alone or in combination with vaginal cuff brachytherapy and/or with chemotherapy among other approaches [5,65,66,70]. In general, UCCC has been underrepresented in these trials with the recently completed PORTEC-3 being one of the exceptions with nearly 10% of patients having UCCC [6]. Three-hundred and thirty of 660 eligible women (50%) were randomized to the pelvic radiation therapy alone arm of which 325 (98.5%) completed therapy, although 158 women (48%) also received vaginal cuff brachytherapy. The primary analysis reported an 76.7% five-year OS (95% CI, 72.1–81.6%) for radiation alone which was similar to the chemoradiation survival of 81.8% (95% CI, 77.5–86.2%) ($p = 0.109$). However, PORTEC-3 included patients with early and advanced stage disease, as well as patients with UPSC. As a result, the trial results did not allow for more concrete therapy recommendations for the use of radiation in advanced stage UCCC. Unfortunately, in spite of a relatively large

Table 3
Impact of stage on administration of adjuvant therapy and death for patients in the National Cancer Database (NCDB) with UCCC (N = 4298).

Stage	N (%)	Receipt of additional therapy (OR) 95% CI	Odds of death (OR)
Stage I or IA	1933 (45%)	Reference	Reference
Stage IB	557 (13%)	2.15 (95% CI 1.74–2.65, p < 0.001)	1.75 (95% CI 1.50–2.04, p < 0.001)
Stage II	442 (10%)	3.28 (95% CI 2.58–4.16, p < 0.001)	1.77 (95% CI 1.50–2.10. p < 0.001)
Stage III, IIIA, IIIB	492 (11%)	2.82 (95% CI 2.25–3.54, p < 0.001)	3.29 (95% CI 2.86–3.80, p < 0.001)
Stage IIIC, IIIC1, IIIC2	799 (19%)	4.62 (95% CI 3.78–5.64, p < 0.001)	3.33 (95% CI 2.94–3.77, p < 0.001)
Stage IVA	75 (1.7%)	4.37 (95% CI 2.48–7.69, p < 0.001)	8.59 (95% CI 6.60–11.18, p < 0.001)

number of UCCC patients in this trial, no specific differences based on this histology were reported to guide the current management of UCCC. We therefore recommend that use of adjuvant radiotherapy in advanced stage UCCC be individualized. For instance, advanced stage patients with disease spread to lymph nodes in the pelvic and para-ortic regions may be more suitable for adjuvant radiotherapy than patients with predominant intra-peritoneal spread.

Question 10: What is the role of multi-modal adjuvant therapy in UCCC?

Multi-modal therapy has been utilized in randomized clinical trials as well as single and multi-institutional series. One of the largest retrospective evaluations was recently published in which the authors evaluated the use of adjuvant therapy in a group of 4298 women from the NCDB [57]. Outcomes in women undergoing hysterectomy were evaluated based on adjuvant therapy, if any, to include chemotherapy, vaginal cuff brachytherapy, external beam radiation therapy or either type of radiation administered in conjunction with chemotherapy. Their study included patients with all stages of UCCC, with the majority 2932 (68.2%) having stage I or II disease. For patients with early stage disease, it was noted that when compared to the referent group of stage I or stage IA UCCC, higher stages were more likely to receive adjuvant therapy, yet in spite of this receipt had inferior OS (Table 3). One inference that could be drawn from this is that stage remains the primary driver of prognosis. Importantly, even the presence of outer one-half myometrial invasion alone, was associated not only with almost a doubling of the likelihood of receiving additional therapy, but with a near doubling in mortality (OR 1.75, 95% CI 1.50–2.04, $p < 0.001$). As evaluated by these investigators, tumor size, race, insurance status and Charlson-Deyo comorbidity scores did not appear to impact receipt of additional therapy, although increasing age as well as distance from treatment centers were associated with a decrease in additional therapy. Impact of multimodal therapy was analyzed in a retrospective study of 80 patients, the majority (70%) of whom either had pure UCCC or UCCC mixed with other histotypes, In univariate analysis, vaginal brachytherapy, whether alone or in combination with other radiation therapy, had an impact on OS (median survival with radiation: 140 months versus without radiation: 50 months; $P = 0.02$), but not on PFS ($P = 0.10$). This association was not noted after testing in a multiple regression model. Adjuvant chemotherapy had no significant impact on OS ($P = 0.26$) or PFS ($P = 0.27$). When patients treated with vaginal brachytherapy plus carboplatin and paclitaxel ($n = 28$) were compared to patients who were not treated with this regimen, no significant difference was seen in OS or PFS ($P = 0.82$ and $P = 0.39$, resp.) [71]. At the present time, there is no prospective data to advocate multimodal therapy in the treatment of UCCC, and retrospective data suggests there is no benefit. We recommend that physicians individualize the use of multimodal therapy based on clinical features and our recommendations in the prreceeding sessions of this document.

Question 11: Are there targeted therapy options for UCCC treatment?

UCCC have a distinct molecular landscape when compared to other endometrial cancers. Previously immunohistochemical studies have compared UCCC with both endometrioid adenocarcinomas and with UPSC. Lax et al. noted the absence of estrogen receptor (ER) and progesterone receptor (PR), as well as low reactivity for p53 and a high Ki-67 index [72]. Interestingly, while the low expression of ER and PR with an increased Ki-67 expression was similar to UPSC, the lack of p53 expression was distinct for UCCC. Secondary to the observation that HER-2/neu was associated with a poorer prognosis in both breast and ovarian cancer, it was evaluated in a pathologic series of endometrial cancers. Rolitsky and colleagues from the Ohio State University evaluated 72 endometrial cancers of varied histologic subtypes, stages and grades for the presence of Her-2/neu amplification via fluorescence in situ hybridization and protein overexpression [73]. Although again underrepresented, all three clear cell cancers exhibited either Her-2/neu amplification via fluorescence in situ hybridization and/or protein overexpression, with amplification appearing to be associated with a worse survival even when considering histology, stage and grade. As noted previously, the work by Zorn et al. suggested that rather than consider the organ of origin in order to determine adjuvant therapy, that perhaps, clear cell carcinomas should be treated in a manner that is agnostic to their organ of origin [18]. Accordingly, when considering that ARID1A has been implicated in carcinogenesis in ovarian clear cell carcinoma, and to a lesser degree with endometrioid ovarian carcinomas, which have both been associated with endometriosis, it is important to determine if similar findings are present in UCCC [74,75]. To this end, Heckl and colleagues evaluated the potential impact of ARID1A, p53, p16 and p21 and beta-catenin in clear cell and endometrioid carcinomas of both the ovary and uterus [76]. This study included nearly 100 tumors, including 17 clear cell tumors of which six were UCCC with the remaining 80 being a mix of endometrioid tumors, which were evaluated and noted to have dissimilar expression profiles. Not only were UCCC vastly different in terms of their IHC expression from endometrioid uterine cancers, they were also dissimilar to ovarian clear cell carcinomas.

While chemotherapy and targeted therapy trials in UCCC are lacking, a clinical trial targeting ovarian clear cell carcinoma has been performed and is perhaps informative. Chan and colleagues performed a two-stage Phase 2 trial, GOG 254, in patients with persistent and/or recurrent ovarian clear cell carcinomas utilizing sunitinib [77,78]. Unfortunately, in spite of a strong scientific rationale, the response rate was only 6.7% (90% CI, 1.2–19.5%) with a median progression free survival of only 2.7 months. While not directly proving that targeted therapy will or will not work in UCCC,

the results from Chan and colleagues perhaps suggest that the presence of a potential molecular target alone is not sufficient in these partially related, yet distinct tumors. Molecular profile permitting, targeted options should be explored in women with UCCC especially in those with recurrent disease where other options have been exhausted or are limited.

Question 12: What are chemotherapy options for treating recurrent UCCC?

UCCC in addition to UPSC, carcinosarcoma and undifferentiated/dedifferentiated uterine tumors are all considered high-risk for both metastasis at time of presentation as well as recurrence [41]. Accordingly, systemic therapies for use in the recurrent setting are also generally homogenous, although certain regimens are preferred based on histologic subtypes. When considering previous experience regarding chemotherapy recommendations for UCCC in the recurrent setting, most data has been obtained by retrospective review of both single institution as well as multi-institutional series in order to attempt to determine optimal therapy regimens. McMeekin's pooled analysis included over 1200 women treated on one of four GOG doxorubicin-based chemotherapy trials for advanced and/or recurrent endometrial cancer, however, a mere 44 patients (3.7%) with UCCC [4] were included. While underpowered for a definitive conclusion based on the low number of cases, UCCC histology did not appear to predict response to chemotherapy, HR 0.59 (95% CI 0.30–1.17, $p = 0.13$), it did predict both a higher risk of recurrence, HR 1.52 (95% CI 1.11–2.09, $p = 0.009$) as well as death, HR 1.51 (95% CI 1.1–2.07, $p = 0.01$) despite receiving adjuvant chemotherapy. Not surprisingly, when evaluating outcomes in addition to the lowest response rates, UCCC had the worst measured survival with a median PFS of only 3.3 months and an OS of 7.9 months. Importantly as noted, the rarity of UCCC will likely preclude future clinical trials limited to UCCC, with UCCC being relegated to comprising but a small minority of prospective clinical trial enrollment. Therefore chemotherapeutic options will continue to be driven by studies with dominant population of participants enrolled from the more common histotypes. Bevacizumab, temsirolimus and ixabepilone have all been shown to have single agent activity in recurrent endometrial cancer. These 3 novel agents were combined with carboplatin and paclitaxel in a 3 arm randomized phase II trial which enrolled 349 patients with advanced or recurrent endometrial cancer [79]. Approximately 4% of these patients had UCCC. The primary end point, PFS was not significantly increased in any experimental arm compared to historical controls. Importantly, in terms of guiding treatment options for recurrent UCCC, Kobel and colleagues noted that 27 of 41 cases (66%) of mixed endometrioid and UCCC had mismatch repair (MMR) protein deficiency which may not only allow the identification of Lynch syndrome, but perhaps selection of immunotherapy in the recurrent setting [80]. Standard treatment for recurrent UCCC remains carboplatin and paclitaxel, when this combination fails or cannot be used, other options include clinical trial enrollment, single agent chemotherapy such as adriamycin and in appropriately chosen patients, immunotherapy such as pembrolizumab.

Question 13: What is the role of surgery in the treatment of recurrent UCCC?

The impact of surgery for recurrent UCCC is poorly described in the literature. Current NCCN recommendations note that surgical exploration with resection may be considered for patients with recurrent disease, although the recommendations do not specifically provide details per histologic subtypes [41]. Italian investigators recently reported on the potential utility of a secondary surgical resection in women suspected to have recurrent endometrial adenocarcinomas [81]. Although the results for this retrospective review were overall encouraging with a five-year OS reported to be 51%, with 40 of 64 patients (63%) receiving post-operative therapy which included either chemotherapy and/or radiation, only two of these patients had UCCC. Moreover, in spite of the absence of definitive data demonstrating the potential benefits of surgery in the recurrent setting, the Gynecologic Cancer InterGroup has noted that consideration for surgery or radiation appropriateness should precede decisions on chemotherapy [82]. We therefore recommend that surgical option should be carefully considered in appropriate patients diagnosed with recurrent UCCC.

Question 14: What is role of radiation in the treatment of recurrent UCCC?

Similar to the role of surgical resection for recurrent UCCC, the use of radiation in the treatment of recurrent disease is fairly limited. Previous commentary has been provided regarding the use of radiation therapy in various modalities from both retrospective as well as prospective clinical trials. Although not traditional radiation per se, Intraoperative radiotherapy (IORT) has been described as a potential modality for consideration in the use of patients with recurrent gynecologic malignancies including endometrial cancer. Krengli and colleagues evaluated the use of IORT in patients with endometrial and cervical cancers mong other malignancies in a systematic review, which was limited by the extreme heterogeneity of the tumor types [83]. Dowdy and colleagues reported on a fairly homogenous group of patients managed by radical resection followed by IORT [84]. Five-year survival was reported to be 41% including two patients diagnosed with recurrence in the para-aortic region, although all patients had endometrioid adenocarcinomas thus perhaps limiting applicability of this approach to those with UCCC. Awtrey and colleagues reported on a very heterogenous series of patients that had radical resection of recurrent uterine cancer, including one patient with UCCC, with both post-operative radiation as well as IORT being utilized in 12 and nine patients respectively [85]. While definitive data is lacking, select patients with recurrent UCCC may benefit from radiation therapy. Appropriate selection is crucial.

4. Conclusions

In summary, UCCC has been and will likely remain underrepresented in randomized controlled trials which are attempting to address ideal adjuvant therapy. Although UCCC have been included and thus evaluated in several trials, histologic underrepresentation precludes definitive conclusions regarding optimal therapy. Collection and evaluation of molecular data, perhaps from future basket trials, may suggest alternative and perhaps novel treatment options. Although a historically high proportion of patients with UCCC enrolled in the PORTEC-3 trial, definitive recommendations remain lacking and unless single histology trials for UCCC are pursued, other clinical trials that allow but do not mandate UCCC seem likely to meet the same fate.

Nonetheless, available information from both retrospective and prospective sources appears to support the following conclusions.

1. UCCC has a higher propensity for extrauterine spread and warrants extended or comprehensive surgical staging, although sentinel lymph node dissection may be a reasonable alternative to complete lymphadenectomy.
2. UCCC is less responsive to chemotherapy when compared to other types of endometrial cancer.
3. We recommend consideration of chemotherapy but also recommend development of clinical trials to further evaluate the role of chemotherapy for early stage UCCC.

4. Vaginal cuff brachytherapy may offer a benefit in outcomes for women with early stage UCCC.
5. Patients with advanced stage UCCC should be offered adjuvant therapy, although evidence for UCCC-specific adjuvant therapy is lacking.
6. In spite of a higher probability of receiving adjuvant therapy than other types of uterine cancer, both PFS and OS for UCCC appears to be inferior thus further solidifying UCCC as an aggressive histology with unique and largely unknown profile.
7. Future clinical trials should continue to allow UCCC enrollment with this and other high risk histologies utilized as a stratification variable.

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Author contributions

Drs. Olawaiye and Leath participed equally in all of the following for this manuscript: Formulation of research question, literature review, data collection, manuscript drafting, and critical revision.

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