



Review

Uterine carcinosarcoma: A review of the literature

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HIGHLIGHTS

- UCS is an aggressive de-differentiated endometrial carcinoma with its own molecular profile.
- Surgical staging and adjuvant chemotherapy are crucial for all stages of disease.
- Future study should focus on UCS specifically and consider targeted therapies.

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ABSTRACT

Objective. Uterine carcinosarcomas (UCSs) are aggressive tumors previously considered to be sarcomas, but now recognized as malignancies composed of metaplastic transformation of epithelial elements. Much of the management for UCS has been extrapolated from studies of endometrial carcinomas and sarcomas. This article critically reviews the literature pertinent to the pathology, pathogenesis, diagnosis and management of women with UCS.

Methods. MEDLINE was searched for English language literature on UCS with a focus on the past 20 years. Given the rarity of this tumor, studies were not limited by design or number of reported patients.

Results. UCS is biologically a de-differentiated endometrial carcinoma with its own pathogenesis and molecular profile. It commonly presents with extrauterine disease which can be identified by comprehensive surgical staging. Most UCS patients are candidates for adjuvant chemotherapy. The role of radiation is less clear. Combination therapy, while commonly used, has not been studied in depth. The high recurrence rate and poor overall survival for UCS suggest an ongoing need for clinical trials for UCS specifically.

Conclusions. UCS represents a distinct subtype of uterine malignancy, and should be studied as such via focused clinical trials.

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1. Introduction

Uterine sarcomas are rare tumors that comprise a diverse group of aggressive malignancies. Of the 52,630 cases of uterine cancer that occurred in the United States in 2014, only 5–6% were classified as uterine sarcomas [1,2]. Uterine carcinosarcoma (USC) has traditionally been included in the sarcoma category, and as such is the most common of the uterine sarcomas; it is also called malignant mixed mesodermal tumor or malignant mixed Mullerian tumor (MMMT). More recently, however, UCS has been categorized as a high grade endometrial cancer (EC). While rare, representing less than 5% of all uterine tumors [3–5], UCS accounts for 15% of all deaths caused by uterine corpus malignancy [6].

UCS is a malignant neoplasm that is composed of both epithelial and mesenchymal elements. Traditionally, UCS was believed to behave as a sarcoma, and therefore was included in clinical trials and treatment protocols that followed sarcoma guidelines. The emergence of more molecular and genetic data has demonstrated that USC is distinct from other sarcomas, and that it is the carcinomatous component that is the primary driver of tumor aggressiveness. Most recent data suggest that the origin of UCS is monoclonal [7–10] and that these tumors are best classified as de-differentiated carcinomas of the endometrium rather than as sarcomas [11]. As a result, UCS is now classified for staging purposes with carcinomas of the endometrium [12].

UCSs are very aggressive tumors. Unlike endometrioid endometrial cancer, where most tumors are of early stage and low grade, UCS presents with extrauterine disease in 60% of cases, and recurrence will occur in more than 50% despite surgery and adjuvant therapy. When compared to high grade endometrial carcinomas, multiple studies have demonstrated that UCS is a far more aggressive tumor [13–16]. The estimated 5-year survival for patients with USC is poor, ranging from 33–39% [17,18] (Table 1). Even in cases where disease is apparently confined to the corpus, the rate of recurrence is high [19,20].

The high recurrence rate and poor overall survival for UCS suggest the need for improved management strategies. Given the rarity of UCS, however, attempts to conduct prospective trials to establish treatment regimens, particularly in the setting of apparently uterine-confined disease, have been challenging. This article is based on a comprehensive review of the published literature with the intent of offering clinicians an overview of the pathology and pathogenesis, epidemiology, presentation, and management of women diagnosed with UCS.

2. Methods

For this article, we reviewed the English language literature for studies on uterine carcinosarcoma. A MEDLINE (PubMed) search of the English literature was performed, with a focus on papers published in the last two decades. Keywords included “uterine sarcoma,” “endometrial sarcoma,” “carcinosarcoma,” “mixed Mullerian” and “mixed mesodermal.” Additional publications were identified via systematic review of all

reference lists within publications retrieved from the MEDLINE search. Given the rarity of this tumor, and the resulting dearth of prospective data, all peer-reviewed original report publications with an appropriate number of cases were considered and included. In studies inclusive of all uterine sarcomas, subset analyses specific to UCS were extracted. Similarly, in studies inclusive of both ovarian and uterine carcinosarcomas, data were extracted specific to the uterine tumors. Finally, some studies of endometrial cancers that included UCS were considered.

2.1. Epidemiology

UCS accounts for 4.3% of all uterine corpus cancers [21]. The worldwide annual incidence is 0.5–3.3 cases per 100,000 women [2].

UCSs and endometrial adenocarcinomas share some similar risk factors (Table 2). Like endometrial adenocarcinoma, UCS risk is increased in the setting of increased estrogen levels and decreased by a history of oral contraceptive pill use. Other common risk factors include nulliparity and obesity [22]. However, there are also some very important epidemiologic differences. When compared to grade 3 endometrioid endometrial carcinomas, women with UCS are older, with a median age of 70 years [16]. They are more commonly African-American, and more often present with advanced disease [16].

Black race is a significant risk factor both for development of UCS and for poor survival. The relatively higher incidence of both UCS and leiomyosarcoma in black women when compared to white women was first noted by Harlow in 1986 [23] and confirmed by Platz and Benda, who also noted that black women were more likely to be diagnosed with advanced disease than white women [24]. A recent SEER analysis confirmed these reports: the overall age-adjusted incidence for black women was twice that of white women and more than twice that of other races [2]. With respect to survival, analysis of the results of GOG 150 (a Phase 3 randomized study of whole abdominal radiotherapy (WAR) versus combination ifosfamide-mesna with cisplatin in optimally debulked stage I–IV UCS) demonstrated no difference in survival between black and white women with advanced stage disease [25]. However, when only early stage disease was considered, both progression free and overall survival were significantly worse in black women. Moreover, on multivariate analysis, black race remained independently associated with risk of death (HR 2.0, 95% CI 1.25–3.23) [25].

Tamoxifen use and prior pelvic radiation have both been associated with the development of UCS. Multiple small series have reported patients who developed UCS following prolonged use of tamoxifen [26]. In one study, the median length of exposure to tamoxifen was 9 years (5–20), and the median time from the initiation of tamoxifen to the diagnosis of the uterine malignancy was 9 years (7–20) [27]. Prior pelvic radiation has also been identified as a risk factor for the development of UCS. A series of 23 patients who developed uterine

Table 1
Recurrence and survival rates by stage including new FIGO staging.

	Recurrence rate [93]	5 year survival [93,98]
Stage I	37%	59–65%
Stage II	46%	45–59%
Stage III	63%	22–26%
Stage IV	80%	9–26%

Table 2
Comparison of epidemiological risk factors between endometrial cancer (EC) and UCS [2,16,26].

Low risk EC	High risk EC	UCS
Estrogen/obesity	Estrogen	Estrogen
Caucasian	African-American	African-American
Nulliparity	Nulliparity	Nulliparity
Tamoxifen	Tamoxifen	Tamoxifen
		Pelvic radiation

EC = endometrial cancer, UCS = uterine carcinosarcoma.

cancer following pelvic radiotherapy was reported; 35% of these were UCS compared to a baseline rate in the authors' population of 6% [28].

The possible contribution of a BRCA1 mutation to the development of UCS was suggested in an abstract presented at the Society of Gynecologic Oncology (SGO) meeting in Tampa, Florida in 2014 [29]. The authors followed 525 women with BRCA mutations who underwent risk reducing salpingo-oophorectomy for a median of 5.8 years. Overall, 4 women were diagnosed with uterine cancer (expected 1.95), and all 4 cases were high risk (expected 0.28): two serous cancers, one UCS and one leiomyosarcoma. While this data is provocative, it is also preliminary and perhaps best considered as hypothesis generating. UCS has also been reported in connection with a familial germline *MLH1* gene mutation resulting in loss of *MLH1* protein expression [30].

Independent predictors of improved survival have been identified. These include: age < 40, white race, the utilization of post-operative radiotherapy, undergoing lymphadenectomy, and early stage of disease [31].

2.2. Pathogenesis

As noted above, UCS was traditionally characterized and studied as a sarcoma, but current data supports a single cell progenitor for UCS and the categorization of UCS as a subtype of endometrial carcinoma [11,32]. There are 2 populations of cells within UCS: a carcinomatous or epithelial component (the main element) and a sarcomatous or mesenchymal component. The sarcomatous portion can be either homologous (uterine type tissue) or heterologous (non-gynecologic tissue, most commonly bone or cartilage). Heterologous types of UCS were previously believed to be more aggressive but contemporary studies have not supported this theory [33]. The epithelial component is usually high grade and it remains debated whether the most common component is serous or high-grade endometrioid [34–37]. Regardless, it is the epithelial component that usually metastasizes and recurs [38,39].

There have been multiple theories regarding the origin of UCS. The interested reader is directed toward the references for more details on the collision and combination theories for historical interest [11,32,40,41]. The currently accepted theory is the 'conversion theory': that UCS originates from the metaplastic transformation of a single cell. This theory is supported by data showing similar chromosomal aberrations, cytogenic aspects, concordant loss of heterozygosity, identical p53/Kras mutations and matching X-inactivation patterns [8,42,43]. Interesting data published by Kalluri and Weinberg suggest that the UCS cells have the phenotypic plasticity to experience not only an epithelial-mesenchymal transition (EMT) but also a mesenchymal-epithelial transition (MET) [44]. These data could explain the aggressive clinical nature of UCS, if cells have the ability to be independent of basement membrane signals and to convert between cell types.

The unique molecular characteristics of UCS are far from understood (Table 3). UCS does not frequently overexpress PTEN, B-catenin or MMR as is common in "type I" endometrial tumors, but does commonly have TP53 mutations (up to 60%) [45]. Most UCS have extreme chromosomal instability with complex karyotypes [9]. Multiple researchers have shown that UCS has an activated AKT pathway via several growth factors (EGFR 1 and 2; ER/PR; IGF1 and 2) [46–48] and 15%–19% of

cases of UCS were noted to have PIK3CA/AKT mutations. Approximately 24% have KRAS mutations [49,50].

Studies of the molecular mutations in UCS involve small numbers of cases and thus are difficult to generalize for targeted study. There are however some potentially "targetable mutations" that have been identified. For example, UCS has been shown to over-express PARP 1, supporting the concept of clinical trials with parp inhibitors [51,52]. Another area of clinical research focuses on the finding that a proportion of UCS has amplification of ErbB-2 (Her2/Neu). The augmentation appears to be mainly in the epithelial component of 14–30% of primary tumors and possibly a greater proportion of recurrent tumors, suggesting that Her2-directed therapies such as trastuzumab may play a role in the treatment of selected cases of UCS [46,53–56]. COX-2 expression was noted to be elevated in 48% of 27 patients with UCS, but did not appear to be associated with prognosis or survival as has been demonstrated in breast and colon cancers. Interestingly, the median survival of UCS patients with high IHC staining scores for COX-2 was longer than those with a lower score (64 versus 25 months, p = 0.4), but this was not a statistically significant difference [57]. VEGF expression was detected in 100% of the epithelial component and 93% of the stromal component of 30 patient samples, suggesting a possible role for VEGF inhibition in therapy [6]. Finally, the prevalence of aberrations in the PIK3CA/AKT pathway in UCS suggests the possibility of successful mTOR inhibition [49].

2.3. Diagnosis

UCS presents similarly to other uterine adenocarcinomas. Most commonly a patient with UCS is postmenopausal with bleeding, abdominal pain and uterine enlargement. While endometrial sampling usually identifies a malignancy, it does not always confirm UCS. UCS may present as an endometrial mass on ultrasound or as a mass prolapsing from the cervix. Because patients with UCS commonly have extrauterine disease at presentation, practitioners may utilize imaging with CT or MRI prior to surgery to help guide patient counseling and surgical planning. There are, however, insufficient data to suggest that preoperative imaging is useful or cost effective.

Elevated preoperative CA 125 levels have been shown in a single institution study of 54 patients with UCS to be associated with extrauterine disease (p < 0.001). Also associated with elevated CA 125 was the presence of serous epithelial component (p = 0.005) and deep myometrial invasion (p < 0.001). Elevated postoperative CA 125 level was noted to be associated with poor survival (HR = 5.725, p = 0.009) [58]. These findings were not confirmed by a follow-up study [59].

2.4. Treatment

As UCS is a very rare tumor, it has been difficult to study prospectively. Much of the data available regarding treatment are retrospective in nature. While evidence-based treatment algorithms exist, they are based on small, often retrospective studies, and may be flawed due to the poor reproducibility of this tumor histology among pathologists [52]. Of note, in determining eligibility for trials of UCS, the GOG's pathology review has found presumed UCS to not to meet eligibility in 9–23% of cases [52,60–67]. In general, multimodality treatment is recommended in all but the earliest stage of disease due to the aggressive nature of UCS. However, the optimal therapy is still debated. Many have adopted paclitaxel and carboplatin therapy with or without radiation following primary surgical therapy. Prospective randomized trials of therapy in UCS are detailed in Tables 4 and 5.

2.5. Surgery

Surgical staging including hysterectomy with bilateral salpingo-oophorectomy, lymphadenectomy and consideration of cytoreduction

Table 3
Comparison of molecular features of USC compared with low risk/high risk EC [6,45–52,55,99].

Low risk EC	High risk EC	UCS
PTEN	TP53	TP53
B-Catenin		PI3K/AKT/MTOR
MMR		KRAS
PI3K/AKT/MTOR		PARP1
		VEGF
		COX 2

EC = endometrial cancer, UCS = uterine carcinosarcoma.

Table 4
Prospective randomized trials for therapy of UCS. Adjuvant therapy, early stage disease (stages I–II)^a.

Trial	Arms	PFS	OS
GOG 20 ^b : Postoperative stages I–II; N = 93 [100] (study included all sarcomas)	Surveillance Doxorubicin	40 months Not reached p = NS	55 months 73.7 months p = NS
EORTC 55874 Postoperative stages I–II; N = 91 [92] (study included all sarcomas)	Surveillance Pelvic RT (51 Gy)	4.93 years 6.22 years p = NS	6.78 years 8.53 years p = NS

ND = no difference, GOG = Gynecology Oncology Group, EORTC = European Organization of Research, NS = not significant.

^a Note: Both studies included all uterine sarcomas, number of UCS only is indicated in the Table.

^b GOG 20 allowed patients to receive pre-randomization pelvic RT (38%), 16% were stage II.

(if applicable) are the initial recommended treatment for UCS, provided the patient can tolerate surgery. In the case of advanced disease, given that UCS is a high grade epithelial carcinoma, some practitioners choose to extrapolate from the data on patients with Stage IV endometrial cancer showing that the amount of residual disease effects survival [68–70]. For apparently corpus-confined disease, retroperitoneal lymphadenectomy is important as part of staging of disease for both treatment planning and prognosis, as well as for overall survival.

2.6. Early-stage disease

Complete surgical staging includes: hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymph node dissection. The GOG has demonstrated that 20% of patients with clinical stage I–II UCS were upstaged by lymph node dissection [19]. Similar to endometrial adenocarcinoma, data support a survival advantage for lymphadenectomy, especially in patients with early stage disease [3,71]. Pelvic washings should be obtained, but do not impact FIGO stage [12]. Though some have considered the addition of omental biopsy or omentectomy to staging, this is not a formal recommendation.

Little has been written regarding the mode of surgical staging for UCS; however, it may be reasonable to consider minimally invasive surgery (MIS) in select patients. Multicenter retrospective data have been presented demonstrating that MIS could be used safely in early stage UCS [72]. While UCS patients were eligible for the GOG LAP2 study, these patients represented only 1.6% of those studied in this trial (41 of 2489 patients), and though LAP 2 did support MIS staging in uterine malignancies, concluding that the study “did not reveal any evidence of a particular subgroup that should not be treated with laparoscopy,” there were too few UCS patients to comment on this modality for UCS specifically. Of note, one of the four port site recurrences did occur in a patient with UCS, albeit advanced disease [73,74].

2.7. Advanced-stage disease

Similar to other aggressive subtypes of endometrial cancer, UCS often presents with extrauterine disease. Though the treatment of women with advanced stage UCS will include adjuvant therapy, the initial therapy should usually consist of surgical cytoreduction. Most gynecologic oncologists in the US operate on UCS patients with the goal of optimal cytoreduction; however, the endometrial cancer studies supporting aggressive surgical cytoreduction for this disease did not include UCS, and thus extrapolation of this philosophy to women with UCS is not evidence-based [68,69]. Never the less, a retrospective review of cytoreductive surgery performed in 44 patients with stage III–IV disease demonstrated that complete resection was associated with improved survival (52.3 months vs 8.6 months, $p < 0.0001$), suggesting that extrapolation of the data in endometrial cancer may be logical [70]. In advanced stage disease, there are no data evaluating minimally invasive surgery.

Neoadjuvant chemotherapy has been described anecdotally in UCS but no reported data exist.

3. Chemotherapy

3.1. Early-stage disease

Given the aggressive nature of UCS, even patients with the earliest stage, non-myoinvasive disease may consider adjuvant therapy. In general, the recommendations for adjuvant chemotherapy in this setting are based on limited data that are retrospective in nature.

Cantrell and colleagues retrospectively identified 111 women (85% stage I) with stage I/II UCS via a multi-institutional review [75]. They found that adjuvant chemotherapy was associated with improved progression free survival (PFS) ($p = 0.003$), but overall survival (OS) was improved only in the absence of lymphovascular invasion

Table 5
Prospective randomized Phase 3 trials for therapy of UCS. Adjuvant therapy, any stage disease (stages I–IV).

Trial	Arms	RR	PFS	OS
GOG 150 [93] ^a N = 206 All stages, previously untreated	WAR Ifosfamide + Cisplatin	NR NR	NR	NR
GOG 108 [60] N = 194 Stages III/IV, recurrent	Ifosfamide Ifosfamide + Cisplatin	36% 54%	4 months 6 months RR = 0.73; $p = 0.02$	7.6 months 9.4 months RR = 0.80; $p = 0.07$
GOG 160 [65] N = 179 Stages III/IV, recurrent	Ifosfamide ^b Ifosfamide + Paclitaxel ^b	29% 45%	3.6 months 5.8 months	8.4 months 13.5 months
GOG 261 ^c Stages I–IV Recurrent, chemo-naïve	Ifosfamide + Paclitaxel Carboplatin + Paclitaxel	Pending	Pending	Pending

RR = response rate, NR = not reported, GOG = Gynecology Oncology Group, WAR = whole abdominal radiation.

^a After adjusting for age and stage, recurrence risk and death rate of those on chemotherapy were 29% lower than those that received WAR (HR 0.79 [0.53–1.176] $p = 0.245$).

^b Patients received up to 8 cycles of chemotherapy.

^c GOG 261 allowed pre-enrollment RT (RT or vaginal brachytherapy).

(LVSI) ($p = 0.01$). Eighteen percent (4 of 22) of women with stage IA (non-myoinvasive) disease recurred without chemotherapy, only 1 of which had LVSI. As expected with retrospective data, the chemotherapy regimens used in this study varied, but the majority were platinum-based [75]. Similarly, data supporting chemotherapy for early stage disease were published by Leath et al., who reported an approximately 50% rate of recurrence in conservatively managed, surgically-staged I UCS, even in stage IA UCS patients, and found that poorly differentiated epithelial or papillary serous histology was the only variable associated with disease recurrence ($p = 0.04$) [76].

The regimen of chemotherapy recommended for use in early stage disease is the same as for late stage disease. The progression of understanding of the appropriate chemotherapy regimen is discussed in the section below on advanced-stage disease. Given the rarity of UCS, there have not been any prospective trials specifically regarding the optimal therapy of early stage disease, although both GOG 150 and 161 did include stage I, including non-myoinvasive, UCS.

3.2. Advanced-stage disease

For patients with advanced-stage disease, adjuvant chemotherapy is recommended. The optimal chemotherapeutic regimen is still debated, and as mentioned previously, much of the early data included UCS with other sarcomas. Contemporary studies either include UCS only or in combination with endometrial cancers. While this change in understanding of UCS has altered the studies in which such patients are included, the effectiveness of chemotherapies can, nonetheless, be discussed.

Originally, single agent chemotherapy regimens were studied. Ifosfamide had the best single agent response rate (36%) [60] as compared to etoposide (6.5%) [61], doxorubicin (9.8%) [62], cisplatin (18%) [77], paclitaxel (18%) [63] and topotecan (10%) [64]. The finding of ifosfamide's superior response led to studies evaluating ifosfamide in combination. First, ifosfamide and cisplatin were compared to ifosfamide alone. While there was an increase in response rate (RR) with the combination (36% versus 54%), there was no significant change in median survival (7.6 versus 9.4 months; $p = 0.07$) and increased toxicity was noted in the combination arm [60]. In contrast, the next study of ifosfamide combination chemotherapy did show a clear survival benefit: Homesley et al. showed that the combination of ifosfamide and paclitaxel was superior to ifosfamide alone and improved median overall survival from 8.4 to 13.5 months ($p = 0.03$) [65].

Despite these data, many oncologists found ifosfamide to be difficult to administer due to toxicity and schedule and the search for other, less toxic regimens continued. Paclitaxel and carboplatin, a relatively well-tolerated regimen familiar to gynecologic oncologists, were noted to be effective in retrospective studies [78,79] and thus several Phase II studies evaluating this regimen were designed [34,66,80]. In GOG 232B, 46 patients were treated with paclitaxel and carboplatin and had a 54% overall response rate (ORR) with 13% having a complete response (CR) [66]. Similarly, Lacour reported a trial of 23 UCS patients with a 62% RR to this regimen [80]. These studies were the rationale behind the study design of GOG 261, a Phase 3 randomized trial of ifosfamide and paclitaxel versus carboplatin and paclitaxel; the study closed in March 2014 and the final results of this study are not yet mature. It should be noted that GOG 261 allowed pre-enrollment RT (either RT or vaginal brachytherapy); see discussion regarding radiation below. In practice, many physicians have made the switch to paclitaxel and carboplatin while awaiting the results of this important study.

Patients with recurrent or persistent disease following chemotherapy have a grim prognosis, as evidenced by the statistical assumptions in the GOG 230 queue for these patients: standard is a 5% response rate and the probability of 6 month PFS is 15%. Cytotoxic agents studied in the GOG Phase 2 UCS queues include: trimetrexate, docetaxel with gemcitabine, and ixabepilone; none have defeated the null hypothesis.

It is likely that further improvement in outcome will be related to the identification of targeted therapy. Initial attempts at targeted therapies have been directed at the findings of molecular abnormalities described above and have had disappointing results. In a Phase II trial of iniparib, a purported PARP-1 inhibitor, combined with paclitaxel and carboplatin, there was no increased response rate [52]. While this result was disappointing, further study has shown that iniparib may not be a selective inhibitor [52]. Similarly, Nimeni and colleagues described the use of sorafenib, a tyrosine kinase inhibitor, in 16 patients with UCS and none had an objective response [81]. Aflibercept (VEGF-Trap), imatinib and pazopanib have similarly had poor efficacy in Phase II trials [67,82,83]. Trastuzumab-EM-Tansine was shown to have activity against HER2+ UCS cell lines [84] but clinical data do not exist. The MTOR inhibitor AP23573 was used in UCS as part of a Phase 2 endometrial cancer study, but none of the responses seen were in the UCS patients [85]. Research continues in these areas.

4. Radiotherapy

4.1. Early stage disease

Salazar et al. first described the results of adjuvant pelvic radiotherapy (RT) for uterine sarcomas in general [86]. Since that initial report, several small retrospective series have examined the role of RT in UCS specifically [87–91]. While most studies demonstrate an improvement in local (pelvic) control in well-staged women with early stage UCS, RT does not seem to confer a survival advantage [88].

A SEER study of 1819 women with early stage (stages I–II) UCS was able to demonstrate that pelvic RT was associated with a 21% reduction in cancer specific mortality [31]. However, among patients with UCS who underwent lymphadenectomy, the survival advantage from radiotherapy was not significant. For patients who did not have lymphadenectomy, radiation was associated with a 25% reduction in mortality. (It is also interesting that this analysis noted that women older than 65 years and black women were less likely to receive adjuvant radiation therapy.) In contrast to the SEER study, smaller retrospective analyses have shown a survival advantage to lymphadenectomy but no survival advantage to the addition of RT with or without a lymph node dissection [71].

The European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group study (EORTC protocol 55874) was a prospective Phase 3 randomized trial designed to evaluate the role of adjuvant pelvic RT for early stage uterine sarcomas [92]. This study opened in 1987 and accrued 224 patients over 13 years, 91 of whom had UCS. Patients were randomized to either observation or pelvic radiation. For the UCS patients, there was a trend toward better local control (in contrast to LMS patients) but there was also a higher distant metastatic rate, and no difference in overall survival. Of note, only 25% of patients underwent lymphadenectomy in this study. UCS patients were not included in the PORTEC studies or in GOG 99, all of which were designed to study adjuvant radiation in intermediate risk endometrial cancers.

In summary, adjuvant pelvic RT appears to decrease the risk of pelvic recurrence and may delay the appearance of distant metastases in patients with early stage disease [87]. However, there remains a high rate of distant recurrence, indicating the need for systemic therapy.

4.2. Advanced disease

The role of RT as a single modality in the setting of advanced UCS is limited. GOG 150, a Phase 3 prospective trial, randomized women with all stages UCS between whole abdominal RT, encompassing the entire abdomen and pelvis, and chemotherapy post surgery; more than half of the patients on study had advanced (stage 3 or 4) disease and 5% had gross residual disease following surgery [93]. In this study, 206 eligible patients were enrolled over 12 years and 105 randomized to

receive whole abdominal RT. The patients who were treated with chemotherapy were more likely to experience a vaginal recurrence, while the patients in the RT group were more likely to experience an abdominal recurrence as well as serious late adverse events, but overall recurrence rate and overall survival were the same for both groups. Of note, the study prescribed only three cycles of chemotherapy, and it is possible that more cycles of chemotherapy would have provided a more demonstrable benefit of chemotherapy over whole abdominal RT.

A retrospective study considered chemotherapy-based versus RT only adjuvant treatment for all stages of UCS; 59% of patients in this series had advanced disease and the majority of patients were treated with chemotherapy or a combination of chemotherapy and RT [94]. Only 11 of 49 patients were treated with RT alone and 91% of these women experienced recurrent disease. As in GOG 150, abdominal recurrences were more common in the group of patients treated with RT alone when compared to those patients who received chemotherapy. Thus, it does not appear that RT alone is sufficient adjuvant therapy for advanced stage UCS.

4.3. Combination therapy

The lack of prospective data demonstrating dramatic control of disease with chemotherapy alone—52% relapse rate at 5 years in GOG 150—has led many practitioners to consider a combination of radiation and chemotherapy following primary surgery. The ideal sequencing of treatment, however, remains controversial. While some investigators have argued that delivering the chemotherapy first in the sequence allows greater likelihood of delivery of all planned cycles, others have advocated the “sandwich” approach of three cycles of combination chemotherapy, followed by consolidation directed RT (either pelvic RT or tumor-directed RT), followed by three more cycles of combination chemotherapy. While most of the literature on combination therapy is retrospective and excludes UCS [95,96], a Phase 2 prospective trial of sandwich therapy specific to UCS has been reported [97]. The regimen in this study was noted to be efficacious at the expense of significant toxicity. The decision to administer combination therapy over systemic chemotherapy for advanced disease remains controversial.

In general, it is reasonable to treat women with completely resected early stage (stage I/II disease) with combination chemotherapy for systemic control, followed by consolidation RT consisting of either vaginal brachytherapy or whole pelvic RT for purposes of local control. For women with completely resected node only disease, the addition of tumor directed RT to the affected nodal beds may be considered, particularly by providers who use this approach for similarly spread endometrial carcinomas. Those women with advanced disease should have combination chemotherapy following surgical cytoreduction. In these situations, radiation can be used for palliation or salvage. It is unlikely, given the rarity of this tumor, that we will have prospective data to guide combination treatment recommendations.

5. Conclusion

Uterine carcinosarcomas are relatively rare but very aggressive tumors that behave like “grade 4 out of 3” endometrial cancers and should be treated as such with complete surgical staging and possibly cytoreduction, as well as aggressive adjuvant therapy in appropriate patients with regimens of chemotherapy with or without RT individualized to the patient and her disease. The understanding that UCS is biologically an endometrial cancer with a de-differentiated component rather than a sarcoma has led to more focused clinical trials and new and more tolerable treatment regimens. Future research should focus on targeted therapies.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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