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Therapeutic Modalities in Early-Stage Uterine Papillary Serous Carcinomas, Carcinosarcomas, Clear-Cell and Mixed Histology Carcinomas: Treatment of Choice Is Combined Chemotherapy and Radiation

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Abstract

The entities covered in this chapter are uterine serous carcinoma (USC), carcinosarcoma, and clear-cell carcinoma together with tumors of mixed histology. Overall, these represent 3–10 % of all endometrial cancers but they are responsible for a significant percentage of endometrial cancer mortality. Recent strides in chemotherapy for some of these cancers offer hope that their addition, either alone or as a part of combined modality treatment including radiation, will lead to improvements in survival.

Keywords

Uterine serous • Carcinosarcoma • Clear cell • Chemotherapy • Chemoradiation

Introduction

Endometrial cancer is the most common gynecologic malignancy being responsible for more than 10,000 deaths in 2015 in the USA [1]. The high-risk histologic subtypes of endometrial cancer, carcinosarcoma, uterine serous carcinoma (USC), and clear-cell carcinoma individually represent 3–10 % of all cancers of the uterine corpus. Although rare, these subtypes have a high risk of local and distant recurrence even when diagnosed at an early stage. Hamilton and colleagues compared 4180 cases of high-risk endometrial carcinoma subtypes. USC and clear cell carcinoma accounted for 10 and 3 % of all endometrial carcinomas, respectively; however, they accounted for 39 and 8 % of all cancer deaths [2]. Treatment schemes for early stage (FIGO I and II), high-risk histologic subtypes of endometrial cancer are variable and include radiotherapy, chemotherapy, or a combination of both. This chapter focuses on therapy for FIGO stage I and II uterine carcinosarcomas, USC, clear-cell and mixed histology carcinomas. Given the low frequency of these malignancies, current treatment recommendations are based largely on multiple retrospective series. There is clearly an ongoing need for randomized controlled

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therapeutic trials for early stage, high-risk histology carcinomas of the uterine corpus.

Uterine Serous Carcinoma

Epidemiology and Natural History

Papillary serous carcinoma was first described as a distinct pathologic entity by two different groups in 1982 [3, 4]. It represents approximately 5–10 % of all endometrial cancers [2, 5–7]. Histologically, it resembles serous carcinoma of the ovary and fallopian tube and behaves like them as it commonly spreads to peritoneal surfaces. In one of the original reports, the relapse rate among stage I tumors was 50 % [4]. Table 1 summarizes the most common clinical findings. The median age at diagnosis is 67 years [5, 7, 8], older than the median age (63 years) of endometrioid endometrial cancer [2, 9]. USC appears to occur more frequently in African American women compared to other ethnicities; in a study by Cirisano et al., the rate of USC was significantly more common in African American compared to Caucasian subjects (34 % vs. 15 %, $P < 0.001$) [7]. Postmenopausal bleeding is the most common presenting symptom, occurring in up to 80 % of patients [5, 10]. Preoperative endometrial sampling demonstrates a serous component in 50–89 % of cases [5, 10–12]. Abnormal cervical cytology (AGUS or worse) is present in approximately 50 % of patients [10, 13]. One study examining all stages of USC found that 13 of 16 (81 %) patients had an elevated serum CA-125 level prior to therapy and that 57 % experienced a reduction or normalization of CA-125 following therapy; however, in another study of 51 patients, only 17 % of patients had an elevated preoperative CA-125 [14, 15]. CA-125 elevation appears to be associated with more advanced stage at diagnosis, positive pelvic node involvement, positive peritoneal washings, and the presence of lymphovascular invasion [16]. A diagnosis of USC should be suspected if >10 % of the preoperative endometrial biopsy specimen contains papillary architecture associated with high-grade cytology. It has been shown that even when 10 % of a mixed tumor contains USC, there is a trend toward decreased overall survival when compared to grade 3 endometrioid adenocarcinomas [17]. While obesity is traditionally considered a risk factor for endometrioid carcinomas, recent studies suggest that obesity is a risk factor for the development of all endometrial carcinomas, including USC [18].

Table 1 Uterine serous carcinoma: Clinical features

Median age at diagnosis = 67 years
More common in African American women
Postmenopausal bleeding common (80 %)
Extrauterine disease at time of presentation (40–70 %)
CA-125 frequently elevated
Endometrial sampling establishes the diagnosis in 50–89 %
AGUS or worse cervical cytology in 50 %

AGUS abnormal glands of undetermined significance

A number of retrospective studies have also suggested an association between USC and breast cancer [19–21]. The evidence is conflicting in regard to the role of tamoxifen in the development of USC [19, 20, 22–28]. Similarly, BRCA1 and BRCA2 mutations have not proved to be strong risk factors for USC, though there is an observed association between USC and breast cancer which may be due to other, yet to be described, cancer predisposing genes [29–34].

As stated previously, USC is a biologically aggressive form of endometrial cancer. It has a different spectrum of genetic alterations than endometrioid-type cancers that contribute to its tumorigenesis. Mutations in p53 and e-cadherin are more common in USC, whereas PTEN inactivation, K-ras mutations, and micro-satellite instability are more common in endometrioid endometrial cancers [35]. HER2/neu overexpression has been reported in 26–62 % of USC and associated with cancer cell proliferation, poor survival, and resistance to therapy [36, 37]. HER2/neu represents a potential target for therapies against USC using antibodies targeting the HER2/neu receptor, such as trastuzumab or pertuzumab. Therapy combining trastuzumab and/or pertuzumab with anti-mTOR, AKT, and/or PIK3CA active agents

may have synergistic activity as HER2/neu is located upstream to the PIK3CA/AKT/mTOR pathway representing possible treatments for USC [38]. It also is unclear whether the expression of HER2/neu or tumoral alterations in the PIK3CA/AKT/mTOR pathway affect recurrence and prognosis in women with early stage USC. The Cancer Genome Atlas Research Network (TCGA) published its findings from the genomic characterization of 373 endometrial carcinomas, which included 66 cases of USC. By unsupervised hierarchical clustering, they found that endometrial carcinomas could be grouped into four distinct clusters. USC (along with a subset of the FIGO grade 3 endometrioid carcinomas) formed a separate cluster which was characterized by a high frequency of TP53 mutations (90 %), fewer PTEN mutations (11 %), and MSI (6 %). This cluster also included other gene amplifications, which included ERBB2, MYC, CCNE1, FGFR3, and SOX17. Tumors in this "serous-like" cluster had a worse progression-free survival than tumors in the endometrioid cluster groups ($P = 0.003$) [39].

Approximately 40–60 % of women with USC will have disease spread outside of the uterus at time of presentation, with extrauterine disease common even in clinical stage I and II [40, 41]. All patients with a suspicion of USC should therefore undergo a surgical staging procedure similar to that employed for early-stage ovarian cancer including TAH, BSO, pelvic and para-aortic lymph node dissection, infracolic omentectomy or omental biopsy, pelvic washings, and diaphragmatic cytology. The additional staging procedures are prognostic but their effect of survival remains unknown. Sentinel lymph node biopsy remains investigational for this high-risk population. Goff et al. reviewed 50 cases of USC and found extrauterine disease in 72 % of them [11]. A large retrospective, single-institution analysis found that among patients without myometrial invasion, 37 % had stage III or IV disease [40]. Chan et al. reported on 12 surgically staged patients (including omentectomy) with USC limited to the endometrium and 50 % were found to have disease outside the uterus (3 of 6 had omental disease). In that series, 1 of 6 (16.7 %) patients with stage IA disease had a distant recurrence [42]. Kato et al. found that when patients had an omentectomy or omental biopsy as part of their initial staging laparotomy, seven of eight (88 %) were positive for malignancy [5]. A similar trend was observed by Cirisano in clinical stage II tumors with 64 % of patients being upstaged at laparotomy [7]. Several series have documented a high frequency of retroperitoneal lymph node involvement ranging from 13 to 33 % [11, 43]. In a prospective randomized controlled trial (ASTEC study), pelvic lymphadenectomy in women with endometrial cancer was not associated with improved survival, but only 4 % of cases had USC and subset analysis was not performed [44]. A study of 84 patients with clinical stage I USC found an overall survival (OS) advantage benefiting women who underwent comprehensive surgical staging compared with those treated only with hysterectomy and bilateral salpingo-oophorectomy (16.4 vs. 2.76 years) [45]. Not surprisingly, one retrospective study identified a 2-year and 5-year overall survival advantage in patients who had complete surgical staging ($N = 21$) versus patients who did not ($N = 17$). The 5-year OS was 95 % in the surgically staged group compared to 45 % in the unstaged group [46].

The contribution of pathologic variables such as lymphovascular space invasion (LVSI), myometrial invasion, and admixture of endometrioid features to overall survival in USC is controversial but are important determinants of the risk of nodal disease. One study of 47 patients found that myometrial invasion, LVSI, or presence of an endometrioid component did not contribute to overall survival [47]. The 5-year overall survival of stage I patients in this series was only 44 %, suggesting that many of these patients were understaged. Goff et al. found that histologic grade and presence of mixed histologic subtypes were not predictive of extrauterine disease [11]. Tumors with LVSI, were more likely to have extrauterine disease (85 %); conversely, even in the absence of LVSI, extrauterine disease was common

(58 %). Kato et al. did not demonstrate an association between myometrial invasion and overall survival, but Slomovitz et al. found that among patients with all stages, LVSI and depth of myometrial invasion were pathologic features that were predictive of overall survival in USC [5, 40]. Another study found that age >60, advanced stage, LVSI, and >50 % myometrial invasion were prognostic factors associated with decreased overall survival [7]. The clinical utility of these pathologic variables has proved to be limited and most patients will need some form of adjuvant therapy [48].

The 5-year overall survival of USC limited to the uterus varies from 34 to 81 % depending on completeness of surgical staging as well as substage [5, 12, 40, 47, 49–51]. In a large, single institution study, the 5-year OS was 81.5 % for patients with stage IA, 58.6 % for stage IB, and 34.3 % for patients with stage IC tumors [40]. In contrast, stage I and II (occult) endometrial adenocarcinomas had 5-year survivals in the 90 % range [52].

One of the contributors to poor overall survival in USC is the high frequency of recurrence in patients with early-stage disease. Recurrence rates in USC limited to the uterus can be as high as 20–50 % [4, 5, 7, 12, 50, 53]. Thus, successful therapy for USC should address both local and distant failures.

Treatment

The aggressive intrinsic biology of USC as well as its high relapse rate in patients with disease clinically (and pathologically) confined to the uterus has led many investigators to suggest the addition of some form of adjuvant therapy regardless of stage. Given the pattern of local as well as distant relapse in stage I and II USC, it appears that combined modality therapy with radiation and chemotherapy would be efficacious. Radiation therapy theoretically would provide local control while chemotherapy would provide distant control. USC has been excluded from most prospective, randomized therapeutic trials of early-stage endometrial cancer because of its uniformly poor prognosis. Therefore, currently, there is a paucity of published randomized-controlled trials demonstrating the efficacy of radiotherapy, chemotherapy, or a combined approach in USC. Additionally, much of the published literature has focused on small numbers of early-stage (I and II) USC and many of these series did not require stringent surgical staging. Therefore, perceived treatment benefits may actually reflect more advanced disease. Despite these limitations, available data reflect a therapeutic benefit to adjuvant treatment in early-stage USC.

Radiotherapy

The role of radiotherapy in controlling local disease and improving overall survival is controversial. The type of treatment modality (whole abdominal radiotherapy, whole pelvic radiation, brachytherapy, or some combination thereof) that is best suited for USC has evolved. For early-stage patients who have had complete surgical staging (TAH, BSO, retroperitoneal lymph node dissection, washings, and omentectomy/omental biopsy), radiotherapy is employed to control local recurrence. Table 2 illustrates a review of studies employing various irradiation treatment types, recurrence rates, and sites of failure.

Given the propensity for USC to recur in the peritoneal cavity, treatment focused largely on whole abdominal radiotherapy incorporating a pelvic boost (WAPI) [49, 51, 54–56]. Kwon et al. reported on 23 women with stage I USC (only one was surgically staged) treated with WAPI, no patients received chemotherapy [54]. Five-year survival was 78.3 % but all recurrences were within the irradiated field. An additional retrospective report by Lim et al. described 43 women with clinical stage I USC treated with adjuvant WAPI, of the 10 patients who recurred, 7 were within the irradiated field [49].

Huh and colleagues reviewed 60 patients with surgical stage I USC (omentectomy was not required) from multiple institutions [57]. Of the

Table 2 Stage I and II USC radiation treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Grice et al. [10]	WPRT/WART	25	Local and distant
Turner et al. [46]	HDR/LDR + WART or WPRT +/− chemotherapy	0	N/A
Bristow et al. [12]	BT/WPRT	16.7	Local
Sood et al. [50]	WPRT/BT	29	Local and distant
Huh et al. [57]	WPRT/BT/WART	16.7	Distant
Hamilton et al. [58]	WPRT/WART	15.4	Local and distant
Sutton et al. [56]	WAPI	42	Local and distant
Thomas et al. [59]	WPRT/WART/BT/Chemotherapy	22	Local and distant

Local recurrences are defined as vaginal and pelvic. Distant failures are either abdominal or extra-abdominal
WPRT whole pelvic radiotherapy, *WART* whole abdominal radiotherapy, *BT* brachytherapy, *WAPI* whole abdominal radiotherapy incorporating a pelvic boost, *N/A* not applicable

40 patients who were observed postoperatively, 7 (17.5 %) had recurrences, 4 locally and 3 distally. Six of the seven patients with recurrence died of their disease. Twelve patients received adjuvant radiation: WAPI in 3, whole pelvic RT (WPRT) and brachytherapy in 5, and brachytherapy alone in 4. Two of 12 patients in the radiotherapy group (16.7 %) had recurrences, and both patients died of their disease. The risk of recurrence and OS were equivalent between those that received either no adjuvant therapy or radiation therapy alone.

The GOG completed a prospective study of adjuvant radiotherapy in women with early-stage USC [56]. Twenty-one women were treated with WAPI consisting of 3000 cGy in fractions of 150 cGy/day to the abdomen and a pelvic boost of 1980 cGy at 180 cGy/day. Eight of 19 evaluable patients died of recurrent disease, 5 of whom had recurrence within the irradiated field.

Given the tendency for USC to recur peritoneally, Fakiris et al. performed a study to evaluate the potential role of adjuvant treatment with intraperitoneal radioactive phosphorus (32P) [60]. Seventeen of the 21 patients were stage I-IIB, and all had undergone comprehensive surgical staging. There were two intraperitoneal and two vaginal recurrences. Vaginal brachytherapy was then added to the regimen and no further vaginal recurrences were noted. Thus, pelvic recurrences appear to be well controlled with the addition of adjuvant pelvic radiation, but distant recurrences are problematic as almost all patients who experience distant recurrences will die of their disease [51, 57, 58, 61]. Interestingly, overall, WART has not been able to control abdominal recurrences [51, 58], moreover, in one study [49], 2 of 58 patients receiving WART for USC died of toxicity potentially related to treatment.

For patients with Stage IA disease (no myometrial invasion), risk of recurrence is lower compared to women with myometrial invasion, 9 % versus 29 %, respectively; therefore, vaginal brachytherapy (VBT) without additional adjuvant treatment has proven successful [53, 62]. In special circumstances, such as no residual disease on surgical specimen at time of complete staging, observation may even be reasonable [61, 63, 64]; however, given the possibility of a lethal recurrence, observation alone should be considered only after careful consideration of risks and benefits to the patient. Given the inconsistent responses achieved with radiation most authors have concluded that other adjuvant approaches, namely chemotherapy, perhaps in combination with radiotherapy, should be evaluated in patients with disease beyond the endometrium.

Chemotherapy and Combined Modality Therapy

The most commonly used adjuvant therapy in early stage USC is carboplatin and paclitaxel, based primarily on retrospective studies and

extrapolating from randomized controlled trials (RCT) in advanced or recurrent endometrial cancer. There are only a few retrospective series that have examined the role of chemotherapy as a single adjuvant treatment modality for stage I and II USC. Table 3 provides a summary of treatment failures in several retrospective adjuvant chemotherapy studies. Sood et al. reported on one patient who received chemotherapy in a population of patients who underwent complete surgical staging. The patient received single agent therapy (doxorubicin, paclitaxel, or cisplatin), recurred distally in the bone, and ultimately died of disease [50]. In the aforementioned study, using platinum-based combination chemotherapy with cyclophosphamide, doxorubicin, or paclitaxel, Huh et al. reported more encouraging results [57]. Of seven patients who received platinum-based chemotherapy as adjuvant treatment, none experienced recurrence over a mean follow-up of 32 months. In a multi-institutional review of surgically staged patients with stage I USC, 21 patients received adjuvant combination chemotherapy with carboplatin (AUC 6) and paclitaxel (135–175 mg/m^2). In this group, there was one vaginal recurrence (salvaged) with a median follow-up of 41 months. Six patients were treated with single agent platinum, and in this group two recurred (33 %) [65]. This study highlights the potential value of adding a taxane to the treatment regimen. Paclitaxel at a dose of 200 mg/m^2 given every 3 weeks has demonstrated activity in advanced or recurrent USC with a reported objective response rate of 77 %, but with significant hematologic toxicity [66]. Another retrospective series showed the potential efficacy of platinum-based combination chemotherapy with paclitaxel. Of six stage I USC patients treated adjuvantly with a platinum/paclitaxel combination, there were no recurrences. One stage II USC patient treated with platinum/doxorubicin failed at multiple sites including vagina and abdomen [58].

Gynecologic Oncology Group (GOG) 209 was a RCT in which women with advanced/recurrent endometrial cancer treated with intravenous (IV) carboplatin/paclitaxel experienced noninferior survival outcomes and significantly less toxicity than women treated with IV paclitaxel, Adriamycin, and cisplatin [67]. Thus, carboplatin/paclitaxel with or without the addition of radiation has become a new standard in the treatment of advanced or recurrent endometrial cancer. Table 4 summarizes early studies of combined modality therapy and treatment failures in USC. In a large study of surgically staged, early-stage USC, Kelly et al. found a statistically significant improvement in disease-free survival (DFS) and OS in patients who received platinum-based

Table 3 Stage I and II USC chemotherapy treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Huh et al. [57]	Platinum combined	0	N/A
Dietrich et al. [65]	Carboplatin/paclitaxel	4.8	Local
Hamilton et al. [58]	Platinum combined	14	Local and distant

Platinum combined refers to cisplatin- or carboplatin-based chemotherapy combined with another cytotoxic agent

Table 4 Stage I and II USC: Combined modality treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Rosenberg et al. [68]	WPRT/platinum combination	0	N/A
Sood et al. [50]	WPRT/single agent	60	Distant
Low et al. [127]	WPRT/BT/platinum combination	7.7	Distant
Kelly et al.[a] [61]	WPRT/WART/BT/platinum combination	4.5	Local
Fakiris et al. [126]	Intraperitoneal ^{32}P/BT	17.6	Local and distant

WPRT whole pelvic radiotherapy, *BT* brachytherapy, *WART* whole abdominal radiotherapy, *Platinum combination* platinum-based regimen with another cytotoxic agent, *Single agent* Adriamycin (doxorubicin), paclitaxel, or cisplatin
[a]Excludes patients with IA disease who did not receive adjuvant treatment

chemotherapy. Seventy-four patients with surgical stage I USC received adjuvant therapy with a variety of adjuvant chemotherapy and radiation protocols. In a multivariate analysis controlled for substage, only chemotherapy with or without vaginal brachytherapy was associated with a significant decrease in recurrences ($P < 0.003$). When broken down by substage, patients with IA disease who did not have any residual tumor in the hysterectomy specimen ($N = 7$) and did not receive adjuvant therapy, none of them experienced recurrences. Among patients with stage IA tumor with residual disease in the uterus at the time of hysterectomy who did not receive adjuvant therapy, 6 of 14 (43 %) had recurrences. The same trend was maintained for patients with stage IB and IC tumors. When combined, 1 out of 22 (4.5 %) patients with stage IB and IC tumors that received adjuvant chemotherapy had recurrences while 14 of 18 (77 %) had recurrences in the no adjuvant chemotherapy group. Interestingly, 5 of 12 (42 %) patients who received brachytherapy alone as treatment had recurrences, but no patient who received radiation (brachytherapy or pelvic) with chemotherapy had vaginal recurrences [61]. Only four of 34 stage I patients experienced a recurrence (11.7 %) after a median follow-up of 58 months, and two isolated pelvic recurrences were salvaged.

In a large retrospective series of stage I patients who had undergone comprehensive staging, patients were treated with carboplatin/paclitaxel with or without addition of radiotherapy. Patients who had received chemotherapy experienced a recurrence rate of 9.2 % compared with 24 % among those patients treated only with radiation and 30 % among those observed ($P = 0.016$). This study also demonstrated a statistically significant improvement in 5-year progression free survival among those patients treated with adjuvant platinum/taxane-based chemotherapy (81.5 %) compared with those observed (64.7 %) or treated with radiation alone (64.1 %; $P = 0.013$) [2].

Furthermore, Fields et al. conducted a Phase II study of patients with USC treated with IV carboplatin/paclitaxel chemotherapy and "sandwiched" whole pelvic radiotherapy demonstrated 3-year OS rates of 75 % for women with early stage disease [69]. The largest dataset supporting the adjuvant use of chemotherapy in stage I serous carcinomas comes from the Uterine Papillary Serous Carcinoma Consortium study [48]. Following surgery, of the 142 women with stage I serous cancer, 23 % received no further treatment, 14 % received adjuvant RT alone, and 63 % were treated adjuvant chemotherapy. Of those receiving chemotherapy (primarily carboplatin and paclitaxel administered for at least three cycles), 37 % also received RT. Those who received adjuvant chemotherapy experienced a statistically significant reduction in the recurrence rate, 11 % versus 30 % in those who received surgery alone and 25 % for patients who underwent surgery followed by RT. Chemotherapy also resulted in a statistically significant improvement in 5-year progression-free survival: 82 % versus 64 % and 65 % in the surgery and surgery with RT groups, respectively. As with most retrospective studies, there is the potential that these results are reflective of selection bias of treatments and particularly, in who did or did not receive chemotherapy.

The largest report on outcomes for women with stage II serous carcinoma also comes from the Uterine Papillary Serous Carcinoma Consortium which included 20 women with stage IIA disease and 35 women with stage IIB disease [70]. Of these, 10 (18 %) were observed following surgery, 19 (34.5 %) were treated with chemotherapy (18 received carboplatin plus paclitaxel), and 26 (47.3 %) underwent RT (though it is unclear if pelvic and/or VBT was administered). Those treated with chemotherapy (19 women) received a range of 3–6 cycles (median = 5). Of the 38 total patients treated with RT (with or without chemotherapy), 34 % received BT, 50 % received WPRT plus BT, and 16 % were treated with whole-abdominal RT alone or in combination with pelvic RT or BT. Patients who received adjuvant chemotherapy, regardless of RT, had a 10 % recurrence rate compared to 50 % in patients not treated with chemotherapy, which was statistically significant. Those who received chemotherapy

experienced a statistically significant improvement in PFS at 5 years (86 % vs. 41 %, respectively) and an improvement in overall survival (OS, 88 % vs. 64 %), although it was not statistically significant.

One of only a few prospective studies, Hogberg et al. [63] reported results of the NSGO trial of radiation alone versus adjuvant chemotherapy before or after radiation in 382 patients with stage I, II, IIIA (positive peritoneal cytology only), or IIIC disease who had high-risk factors for recurrence (one or more of deep myometrial invasion, non-diploid DNA, or serous, clear cell, grade 3, anaplastic histology). Chemotherapy was not standardized and included doxorubicin and platinum (AP); paclitaxel, doxorubicin, and platinum (TAP); paclitaxel and platinum (TP); or paclitaxel, cisplatin, and epirubicin. The study suggested an improvement in progression-free survival with chemotherapy (7 % improvement at 5 years, $P = 0.03$), but survival data were too early to draw any conclusion. Specifically, there did not appear to be any benefit of adjuvant chemotherapy in serous/clear cell carcinomas, though the number of patients was relatively small and the CIs were wide. Hogberg et al. [71] subsequently reported more mature results, and combined the results with a similar study carried out by the Mario Negri Institute (MaNGO) trials group in Italy (ILIADE-III). The two studies included 540 patients with endometrial cancer (FIGO stages I–III) with no residual tumor and randomly allocated patients to adjuvant radiotherapy with or without sequential chemotherapy [71]. In the combined analysis, there was a significant reduction in risk of relapse in the chemotherapy arm (hazard ratio [HR] 0.63, CI 0.44–0.89; $P = 0.009$). Neither trial alone showed any significant difference in overall survival.

Although platinum- and taxane-based chemotherapy is commonly used in patients with USC, there is no prospective data. PORTEC 3 (a randomized, phase III trial comparing concurrent chemoradiation and adjuvant chemotherapy with pelvic radiation alone in high risk and advance stage endometrial carcinoma) and GOG 249 (a phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by carboplatin/paclitaxel in patients with high risk early stage endometrial carcinoma) will hopefully provide important answers in treatment of USC.

Summary

Uterine serous carcinoma is a rare histologic subtype of endometrial cancer, representing approximately 5–10 % of all endometrial cancers but a disproportionate number of deaths due to disease. It is an aggressive tumor with a unique spectrum of genetic alterations contributing to its tumorigenesis [35]. Many retrospective studies have demonstrated a high frequency of extrapelvic disease even in clinical stage I tumors and that tumor spread tends to mimic that of serous ovarian cancer rather than endometrioid endometrial adenocarcinoma. If 10 % or more of the preoperative biopsy specimen contains USC, an extended surgical staging procedure should be performed [17]. Extended surgical staging includes hysterectomy, bilateral salpingo-oophorectomy (BSO) pelvic and paraaortic lymph node dissection, infracolic omentectomy or omental biopsy, and peritoneal cytology and should be performed in all patients with clinical stage I or II tumors.

Multiple adjuvant treatment modalities for early-stage USC have been employed (Tables 2, 3, and 4). Taken together, radiation alone affords some degree of local control while still leaving patients at risk for distant failure. Chemotherapy as a single treatment modality is likely best given as a platinum agent combined with a taxane. Single agent chemotherapy alone is associated with a high rate of distant failures [35]. Combined modality therapy with chemotherapy and radiation appears to offer the lowest recurrence rates with acceptable morbidity. Vaginal recurrences can be significantly reduced with brachytherapy alone [60, 61], with lower morbidity than WPRT or WART. In patients with residual disease in the hysterectomy specimen, it is currently our recommendation to treat all early-stage USC patients with chemoradiation [38, 61]. While paclitaxel/

carboplatin appears to be the optimal chemotherapy, the ideal radiation techniques are still under investigation in studies such as PORTEC 3 and GOG 249.

Clear Cell Carcinoma and Tumors of Mixed Histology

Epidemiology and Natural History

Clear cell carcinoma represents <5 % of all endometrial cancers in the United States. It was first described by Scully and Barlow who identified these tumors to originate from müllerian epithelium [72]. Microscopically, they show tubulocystic, papillary, and/or solid patterns [73]. The clear histologic appearance of the tumor cells is due to their high glycogen content. Other histologic hallmarks are eosinophilic and hobnail cells. All tumors are graded as poorly differentiated (grade 3) by FIGO convention, and unlike clear cell carcinoma of the cervix, in the corpus it does not appear to be associated with maternal exposure to diethylstilbestrol. These cancers have a very similar clinical course to that seen in USC with regard to pattern of spread, lack of apparent precursor lesions, and poor prognosis when compared to endometrioid cancers. Thus, clinical outcomes in clear cell cancers have often been reported in combined series with USC.

Tumors of mixed histology are more common than pure serous or clear cell carcinomas. Craighead et al. reported that 11 % of their patients had tumors of mixed histology including some combination of endometrioid, clear cell, and serous carcinoma [74]. Most reports define mixed histology as the coexistence of two or more cell types each of which constitutes at least 10 % of the tumor. Cirisano et al. found that tumors with mixed histology (at least 25 % of serous or clear cell carcinoma) behave similarly to USC [75]. The amount of unusual histology needed in a mixed carcinoma to confer a poor prognosis is unclear. Some investigators believe that any amount of poor-prognosis histology (serous or clear cell carcinoma) is sufficient, whereas others think that a small focus of high-risk histology does not affect prognosis. It has been demonstrated that if 10 % of the tumor is composed of serous carcinoma, the prognosis is worse than that of poorly differentiated endometrioid adenocarcinoma [17].

Clear cell carcinoma is most commonly seen in thin, postmenopausal patients, is not likely related to estrogen exposure, and is more common in African American women [62, 75, 76]. As with other high-risk types of endometrial cancer, there is a high risk of extrauterine spread. A complete staging procedure is therefore indicated. Cirisano et al. showed that nearly 40 % of patients with clear cell carcinoma clinically confined to the uterus had extrauterine spread and a small number had extrauterine disease even in the absence of myometrial invasion [75]. As with USC, survival is highly variable and depends on the extent of surgical staging with most series not requiring retroperitoneal nodal sampling or omentectomy. Abeler et al. reported the Norwegian Radium Hospital experience with 97 patients diagnosed with clear cell carcinoma and unclear surgical staging [77]. They found a 42 % 5-year survival for all stages of clear cell carcinoma compared to 27 % for USC. The 5-year OS rate was 90 % for patients without myometrial invasion, 59 % for patients with disease limited to the corpus, and 27 % for patients with stage II disease. In this series, myometrial invasion and LVSI were poor prognostic factors [77]. Carcangiu et al. reviewed 29 patients with surgical stage I and II clear cell carcinoma. Eleven of 29 patients had retroperitoneal nodal sampling. The 5-year survival for patients with stage I clear cell carcinoma was 73 % and 59 % for those with stage II tumors [78]. Creasman et al. reviewed the FIGO annual data and reported a 5-year survival rate of 81 % for surgical stage I clear cell carcinoma compared to 72 % for USC and 76 % for grade 3 endometrioid cancers [79]. Large studies of clear cell carcinoma patients in which all have been "comprehensively" staged, including lymph nodes and omentectomy, have not been reported.

Treatment

Given the rarity of these tumors, there are no prospective trials involving only early-stage clear cell carcinoma or mixed tumors. Most trials completed by the National Cancer Institute sponsored Gynecologic Oncology Group (GOG) have only included patients at the point of relapse with measurable disease for salvage chemotherapy. GOG 99, a large prospective randomized trial of intermediate risk (stage I and II) endometrial cancer patients, specifically excluded high-risk histologic subtypes [52]. Our recommendations for therapy must, therefore, be extrapolated from retrospective trials involving heterogeneous cohorts of patients (USC, grade 3 endometrioid, and mixed histology). The initial therapy is surgery with a comprehensive staging procedure including hysterectomy BSO, pelvic and paraaortic lymph node resection, omentectomy, and possibly multiple peritoneal biopsies, and diaphragm cytology. Patients with no residual disease at the time of hysterectomy (high-risk tumor only on dilation and curettage or endometrial biopsy) and possibly other stage IA patients can be observed. All other patients should be considered for adjuvant therapy.

As clear cell carcinoma appears to behave clinically like USC and other aggressive histologic variants of endometrial cancer, we recommend consideration of adjuvant cytotoxic chemotherapy for these patients based on available retrospective data for USC. Unfortunately, clear cell carcinomas are less responsive to conventional cytotoxic chemotherapy than other high-risk histologic subtypes of endometrial cancer. McMeekin et al. reported the GOG experience of 1203 patients with measurable recurrent or advanced endometrial cancer treated with a variety of different regimens (doxorubicin, cisplatin, paclitaxel, or combinations). The overall response rate was 42 % for the entire cohort, being 44 % for endometrioid carcinoma, 44 % for USC, and 32 % for clear cell carcinoma [80]. The decreased response for the clear cell carcinoma tumors was statistically significant. Thus the most appropriate chemotherapeutic regimen is not known and toxicity should be taken into account when selecting adjuvant therapies. Therefore, there may be a role for novel biologic agents in treating this malignancy. Although there is limited data available for patients with clear-cell carcinomas and mixed histology, it is likely that they will benefit from some form of pelvic radiotherapy to decrease the risk of local recurrence. As with USC, chemoradiation is likely to have the lowest failure rates in early-stage clear-cell carcinomas and mixed-histology tumors. Our current recommendation is to use vaginal brachytherapy or intensity-modulated radiation therapy (IMRT) to the pelvis in combination with carboplatin and paclitaxel. This regimen is not based on evidence of superior efficacy to other regimens, but on the manageable toxicity of this regimen.

Carcinosarcoma

Epidemiology and Natural History

Uterine carcinosarcomas represent $\leq$5 % of all endometrial cancers. Like USCs, they are biologically aggressive neoplasms with high rate of extrauterine disease, high recurrence rates (about 50 % across multiple series), and poor disease-free and overall survival rates. Whether carcinosarcomas should be classified as epithelial or mesenchymal tumors has been debated. In most of the clinical literature to date, carcinosarcomas have been included with uterine sarcomas, likely because their prognosis is dismal; however, there is mounting molecular evidence that these tumors are clonal [81–85] and epithelial in origin. The malignant epithelial component has been shown to be capable of inducing a mesenchymal component when injected into nude mice whereas the mesenchymal component could not [83]. Furthermore, patterns of metastases indicate the prominent role of the epithelial component as well. Silverberg et al. found a carcinoma component in 30/34 (88 %) lymph node metastases [86]. Autopsy data, however, have shown no

difference in metastatic spread between uterine carcinosarcomas and leiomyosarcomas [87]. Clinically, carcinosarcoma behaves like a combination of aggressive adenocarcinoma and sarcoma with a propensity for both lymphatic and hematogenous spread and uniformly poorer outcome when compared to other high-risk histologic subtypes of endometrial cancer. Amant et al. compared outcomes among three groups of high risk, early-stage endometrial cancer patients including grade 3 endometrioid adenocarcinomas, carcinosarcomas, USC, and clear-cell carcinomas. Although only 45 % of the patients had lymphadenectomy at the time of staging laparotomy, carcinosarcomas were more likely to spread to pelvic and para-aortic lymph nodes. Long-term survival was 86 % for grade 3 endometrioid adenocarcinomas and 44 % for carcinosarcomas. After a median follow-up of 24 months, 58 % of patients with carcinosarcoma had died of their disease compared to 43 % with USC and clear cell and 28 % with grade 3 endometrioid adenocarcinomas [88].

Uterine carcinosarcomas occur more commonly in older (postmenopausal) patients [89] and a review of SEER data found a higher frequency of carcinosarcomas in African American versus Caucasian women (4.3 vs. 1.7/100,000, $P < 0.001$) [90]. Like most histologic variants of endometrial cancer, carcinosarcomas commonly present with vaginal bleeding or pelvic pain [91]. A summary of common clinical findings is presented in Table 5. Grossly, they often grow as fleshy, polypoid masses filling or prolapsing out of the endometrial cavity. There may be an association between long-term tamoxifen use and development of carcinosarcomas [92]. Complete surgical staging is paramount in these patients. In one study, 32 % of patients with clinical stage I disease (thought to be confined to the uterine corpus) were upstaged based on omental involvement (three of nine patients) or positive lymph nodes [91]. The importance of evaluation of extrauterine disease is highlighted in a landmark clinicopathologic study of 203 early-stage (clinical stage I and II) carcinosarcomas [86]. In this study, 40 patients were identified with metastatic disease. The majority of the tumors (25 out of 40) had >50 % myometrial invasion, but 10 % (4 patients) had no myometrial invasion. Notably, the recurrence rate at 31 months for carcinosarcomas without myometrial invasion was 25 %.

Multiple attempts have been made to identify pathologic variables associated with outcome and the results have been controversial. Because prognosis is poor even in early-stage disease, it is difficult to identify pathologic variables that will be statistically associated with outcome. In a study of 301 stage I and II (clinical) carcinosarcomas, adnexal spread, lymph node metastases, heterologous type of mesenchymal component, and grade of sarcomatous component were all associated with decreased progression-free survival (PFS) [93]. The overall recurrence rate in this study was 53 % and 21 % of tumors recurred in the pelvis. In other longitudinal studies of carcinosarcoma, no significant associations have been found between carcinoma grade, sarcoma component, mitotic count, LVSI, sarcoma histologic subtype, or tumor size and overall survival [91, 94]. It has been argued that prognosis is worse when the epithelial component is a serous carcinoma [95, 96], but this has not been definitively proven. Results from TCGA evaluating mutations, DNA aberrations, and proteomic features should help elucidate the molecular characterization of carcinosarcomas.

Table 5 Carcinosarcomas: clinical features

Median age at diagnosis = 62–67 years
More common in African American women
May be associated with long-term tamoxifen use
Postmenopausal bleeding most common
Grossly bulky polypoid masses

Treatment

As outlined above, uterine carcinosarcoma carries a particularly poor prognosis even when diagnosed at an early stage. Ideally, treatment should address the high rate of both local (pelvic)

and distant recurrences. Because carcinosarcomas are rare, the majority of clinical studies are retrospective. The few prospective, randomized trials include other types of uterine sarcomas or include all stages of carcinosarcomas. Therapeutic trials directed specifically to early-stage carcinosarcoma are rare. Current clinical management of these tumors is therefore evolving and more randomized clinical trials are needed.

Initial evaluation of uterine carcinosarcomas is similar to that for other forms of endometrial cancer. A preoperative chest X-ray should be obtained to rule out pulmonary metastases. Abdominal-pelvic CT scan is warranted if surgical resection does not seem clinically/technically feasible to evaluate disease extent and determine protocol eligibility. Complete surgical resection is advisable including total hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic/para-aortic lymph node dissection and is the primary management of carcinosarcoma limited to the abdomen for both staging and initial treatment [97]. The value of routine omentectomy in carcinosarcomas has not been established, but in the presence of grossly positive lymph nodes, removal/biopsy of the omentum may convey prognostic value. While still investigational, initial data suggest that progression-free survival in women who have undergone sentinel lymph node biopsy is similar to women who underwent routine lymphadenectomy at time of staging [98]. Adjuvant treatment with radiation, chemotherapy, or combination of both is advisable even in early-stage disease. Results from a growing body of evidence suggest that chemotherapy, without adjuvant RT, is treatment of choice for stages IB to IV [99].

Observation for Stage IA

There are low quality data to inform the benefit of adjuvant treatment in patients with disease invading less than half of the endometrium (Stage IA); therefore, observation rather than adjuvant treatment is preferred in some cases because women with stage IA carcinosarcoma have a better prognosis compared with those with IB or later stage disease [100]. In addition, it is unclear adjuvant treatment improves prognosis in these patients [101–103], though some advocate for chemotherapy using a treatment algorithm similar to one used for USC [104].

Adjuvant Radiation

There is only one prospective, randomized controlled trial of adjuvant radiation focused solely on uterine carcinosarcomas (GOG 150). This trial randomized patients with all stages of optimally debulked uterine carcinosarcoma to adjuvant whole abdominal radiotherapy (WAR) or cisplatin 20 mg/m^2 plus ifosfamide 1.5 g/m^2 with mesna for three cycles. Preliminary results suggest improved results for patients receiving chemotherapy [99]. There are multiple retrospective studies analyzing the role of adjuvant radiotherapy in early-stage carcinosarcoma. Although overall survival benefit was identified in a small number of studies, the majority did not require strict surgical staging. Despite these limitations, local control appears to be improved with the addition of WPRT +/− vaginal brachytherapy. A recent study out of Mayo Clinic and Harvard looked at vaginal brachytherapy for early-stage carcinosarcoma of the uterus. This retrospective study included 33 patients from 2 institutions with stage I ($n = 15$) and II ($n = 18$) carcinosarcoma. Eighty-two percent of the patients underwent pelvic LND and 55 % received chemotherapy as well. Two-year vaginal cuff control 94 %, pelvic control 87 %, locoregional control 81 %, DFS 66 %, OS 79 %. Authors concluded that risk of pelvic recurrence was comparable to women treated with pelvic radiation but no lymph node dissection; therefore, pelvic radiation should be considered based on clinical context [105]. Table 6 summarizes recurrence rates in early-stage carcinosarcomas treated with adjuvant radiation.

Gerszten et al. reviewed their experience with 44 early-stage (FIGO stage I and II) uterine carcinosarcomas. Twenty patients received

Table 6 Uterine carcinosarcoma: single modality therapy

Reference	*N*	Modality	Recurrence
Gerszten et al. [106]	20	WPRT +/− brachytherapy	0 %[a]
	24	Surgery	22 % (local and distant)
Knocke et al. [107]	33	WPRT +/− brachytherapy	Local = 4.8 % stage I, 25 % stage II
			Distant = 18.3 % stage I, 33.3 % stage II
Chi et al. [108]	28	WPRT (10 neoadjuvant)	21 % pelvic, 43 % distant[b]
	10	Surgery	50 % pelvic, 40 % distant
Le [109]	12	WPRT	58 %[b]
	16	Surgery	44 %
Omura et al. [102]	93	Adriamycin	38 %[b]
		Surgery	51 %
Sutton et al. [110]	65	Cisplatin/ifosfamide	Overall = 35 %; pelvic = 15.4 %, distant/multiple site = 20 %
Resnik et al. [111]	23	Cisplatin, doxorubicin, etoposide	22 %
Odunsi et al. [112]	8	CYVADIC	38 %
Brown et al. [105]		Brachytherapy +/− chemotherapy	22 %

WPRT whole pelvic radiotherapy, *CYVADIC* cyclophosphamide, vincristine, doxorubicin (Adriamycin), dacarbazine
[a]Significant difference in overall survival favoring radiation therapy
[b]No difference observed in overall survival versus surgery

WPRT with or without vaginal brachytherapy and 24 were managed with surgery alone. Over the whole cohort of all stages ($N = 60$), 73 % had lymph nodes removed as part of the surgical staging. The investigators noted a decrease in local failures (22 % in surgery group and 0 % in RT group) as well as a decrease in combined local and distant failures (32 % and 4 %, respectively). Median survival in the surgically managed group was 12 months compared to 77 months in patients who received adjuvant RT ($P = 0.07$ for all stages). Survival was also improved in patients with stage I and II tumors ($P = 0.02$). In this study, local failure was predictive of distant recurrence and death even when adjusted for clinical stage [106]. Molpus et al. retrospectively examined outcomes in 43 early-stage uterine carcinosarcoma and found a significant survival advantage in patients who were treated with surgery and adjuvant radiation compared to surgery alone. As it has proven typical for this aggressive disease, 29 % of patients with clinical stage I were upstaged at the time of laparotomy and the 5-year OS was only 38 % when the disease was confined to the uterus [113], suggesting that surgical staging was incomplete. Interestingly, a benefit was seen in patients who received RT suggesting that improved local control may decrease distant failure rate. Yamada et al. reviewed 62 patients with clinical stage I uterine carcinosarcoma. Ninety percent of the patients had pelvic lymphadenectomy and 42 % para-aortic lymph node sampling. Of 28 patients who were considered stage I or II, only 11 received adjuvant WPRT. The authors identified an overall survival benefit in these patients, but were unable to show a decrease in pelvic recurrences across all stages. Of note, in this study, occult extrauterine disease was identified in 61 % of 62 patients. The overall recurrence rate was 50 % and 43 % of patients had distal recurrences [96]. Local and distant control was also achieved in a retrospective analysis by Knocke et al. There were 33 patients with early stage tumors (out of 63 reviewed), but only 41 % had some form of lymph node sampling. WPRT +/− vaginal brachytherapy was employed in all patients and local control rates were 95.2 % for patients with stage I and 75 % for patients with stage II tumors. Distant control rates were equally impressive at 81.7 % for stage I and 66.7 % for stage II tumors. Only 3.2 % of patients receiving radiotherapy had grade 3 toxicity [107].

Although these studies demonstrated survival advantage and decreased local and (potentially) distal failures using adjuvant WPRT +/− vaginal brachytherapy, several studies question the therapeutic benefit of adjuvant RT in early-stage uterine carcinosarcomas. Chi et al. reviewed 38 patients with stage I and II carcinosarcomas. Surgical staging was incomplete with only 45 % of patients having some form of lymph node sampling. Out of ten patients managed by surgery alone, 50 % had a pelvic recurrence, 40 % had a distant recurrence, with a 60 % 5-year OS. Out of 28 patients treated with WPRT (10 had RT as neoadjuvant treatment), 21 % had a pelvic recurrence, 43 % a distant recurrence, with a 59 % 5-year OS. Although the overall survival and rate of distant failures were unchanged, pelvic recurrences were reduced by 50 % in the second group [108]. In a review of 32 carcinosarcoma patients (19 stage I and II) with complete surgical staging, Le et al. found similar recurrence rates among those treated with surgery alone or surgery plus adjuvant irradiation; 44 % (7 of 16) in the surgery only group and 58 % (7 of 12) in the surgery plus adjuvant radiation group recurred. Overall survival was equally dismal in both groups with 27 % of patients surviving among those treated with RT versus 33 % of patients who had surgery alone [109]. In another study that examined clinical stage I–III uterine carcinosarcomas, patients who were treated with adjuvant or neoadjuvant (only 35 of 300 patients had surgery followed by RT), WPRT was associated with fewer pelvic recurrences than surgery alone (28 % vs. 48 %, $P < 0.0002$). Pelvic radiotherapy appeared to lengthen the time to distant relapse from 7 to 17 months, but the overall rate of distant failure was similar between surgery and surgery plus radiation groups (54 % vs. 57 %, respectively) [114]. Sartori et al. also found that adjuvant radiation conferred a decrease in the local failure rate but no improvement in overall recurrence rates. Of 66 clinical stage I and II uterine carcinosarcomas, the overall recurrence rates were 38.2 % (stage I) and 63.6 % (stage II). As a combined group, 40 % of early-stage carcinosarcomas failed locally, 40 % failed distally, and 20 % failed at multiple sites. When all stages were included, WPRT reduced pelvic recurrence rates from 21 to 10.7 % in patients who received adjuvant RT [115]. Finally, in one of the only randomized trials conducted in early-stage uterine sarcomas, pelvic radiotherapy appeared to reduce the rate of vaginal recurrences, but was not found to improve distant failure rates even in the doxorubicin (Adriamycin) arm of this trial [102] (to be discussed further in the "Chemotherapy" section of this chapter).

Although the majority of these studies feature admixtures of different surgical stages with a wide variety of therapeutic RT (some neoadjuvant, some adjuvant), it appears that pelvic radiotherapy offers a decrease in local relapse rates. The effect on overall survival varies among studies and will only be adequately addressed in prospective trials. Distant failures are common in patients treated with surgery or a combination of surgery plus irradiation, therefore chemotherapy should be included as part of the adjuvant regimen.

Chemotherapy

As mentioned above, the high-distant failure rate (from 19 to 50 %) across multiple studies in early-stage uterine carcinosarcoma suggests that adding chemotherapy could improve survival. Interestingly, as understanding of the molecular basis of carcinosarcomas has improved, the chemotherapeutic regimens have changed. Initial therapeutic trials assumed that carcinosarcomas behaved clinically like sarcomas and were treated with the same agents. Over time, the epithelial component has been shown to drive tumorigenesis and clinical behavior of this malignancy and therapeutic strategies have shifted accordingly. Although the majority of chemotherapeutic trials include advanced stage patients with measurable disease, it can be extrapolated that agents with activity in advanced or recurrent uterine carcinosarcoma may have activity in early-stage disease as well. A summary of recurrence rates in

patients treated with adjuvant chemotherapy is found in Table 6.

Omura et al. performed a phase III trial of adjuvant Adriamycin (60 mg/m^2) versus observation in patients with clinical stage I and II sarcomas. Lymphadenectomy was not required for surgical staging, but all patients were required to have no residual disease after primary surgery. Pelvic radiotherapy was allowed at the discretion of the treating physician. Of 156 evaluable patients, 93 had a diagnosis of carcinosarcoma. The recurrence rate was 38 % in the adjuvant doxorubicin group and 51 % in patients without further treatment (not statistically different). For clinical stage I tumors, the median survival was 67.2 months. The addition of adjuvant Adriamycin did not prolong OS or PFS, and no difference was seen when a subgroup analysis was performed in patients who received adjuvant pelvic radiotherapy as well. For patients with carcinosarcomas in the doxorubicin arm, 75 % of the recurrences occurred in the pelvis and vagina compared to 33 % in the no chemotherapy arm. Distant metastases (lung and abdomen) were reduced from 66 % in the no treatment group to 25 % in patients treated with doxorubicin. Although no overall statistical differences were seen between treatment and no treatment arms of this trial, there appears to be a trend to reduce distant failure in patients with carcinosarcoma with adjuvant treatment [102].

Other agents have been evaluated as adjuvant therapy in the advanced/recurrent setting. Sutton et al. performed a phase II trial of ifosfamide and mesna in patients with advanced/recurrent uterine carcinosarcoma and found an objective response rate (OR) of 32.2 % with an 18 % complete response (CR) rate. There was one death attributed to therapy among 29 evaluable patients [116]. Sutton et al. also then examined the role of combination chemotherapy with ifosfamide plus or minus cisplatin in a large phase III trial of patients with advanced or recurrent uterine carcinosarcomas. Treatment consisted of 1.5 g/m^2/day ifosfamide for 5 days (a reduced dose was given to patients with a history of radiation therapy) with or without 20 mg/m^2 cisplatin × 5 days. The overall response rate in the combination arm was 54 % compared to 36 % in the ifosfamide alone arm. There was no change in OS with the addition of cisplatin, but a slight prolongation of PFS was observed. The combination regimen was toxic with six treatment-related deaths seen with full (1.5 g/m^2) doses of ifosfamide [117]. Given the improved OR with combination cisplatin and ifosfamide, Sutton et al. examined the same combination regimen in a phase II trial of 65 evaluable patients with clinical stage I and II uterine carcinosarcomas. Lymphadenectomy was not required as part of the surgical staging, and all patients were scheduled to receive three cycles of adjuvant combination chemotherapy. The primary outcome measures were disease-free survival (DFS) and OS. The dosing was similar to the phase III trial [117]. The majority of patients (89 %) completed three cycles. Grade 3 or 4 thrombocytopenia was seen in 63 % of evaluable patients, and 26 % had grade 3 or 4 neutropenia. The 2-year PFS was 69 % while the 2-year and 5-year OS were 82 % and 62 %, respectively. Of the patients that had recurrences (35 % of whole cohort), half of them were in the pelvis [110]. Note that there was no adjuvant radiation allowed in this trial.

Resnik et al. studied combination chemotherapy with cisplatin doxorubicin, and etoposide in 42 patients with uterine carcinosarcoma. In this phase II trial, 23 patients had stage I or II disease. Almost all (22 of 23) patients had complete surgical staging with lymph node sampling with or without omentectomy. Preoperative or postoperative radiotherapy was allowed. Out of the 23 patients with early-stage tumors, 5 had recurrences (22 %). Of note, USC was identified as the carcinoma component in 3/5 (60 %) of the patients with recurrences. In this study, patients with early stage disease had a 92 % 2-year survival rate and an 83 % PFS. Only 22 % of patients experienced grade 3 complications [111]. Other phase II trials in advanced/recurrent carcinosarcoma have not been successful [118, 119].

In GOG 161, Homesley et al. found that adding paclitaxel to ifosfamide improved OS and PFS when compared to ifosfamide alone. In this study, 179 patients with advanced/recurrent

uterine carcinosarcoma were randomized to receive ifosfamide alone at a dose of 2 g/m^2 or ifosfamide at 1.6 g/m^2 plus paclitaxel at 135 mg/m^2 every 21 days for a maximum of eight cycles. The combination arm had significantly better overall response and a 29 % decrease in the adjusted hazard of death or progression ($P = 0.03$), although alopecia and neuropathy were more commonly seen [120]. One retrospective study in patients with advanced/recurrent carcinosarcoma found four of five evaluable patients (80 %) to have a complete response to combination therapy with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) [121]. A phase II trial of paclitaxel and carboplatin in patients with advanced (stage III or IV) disease showed a complete response rate of 13 % (46 patients) and partial response in 41 % with acceptable toxicity[122]. This has led to GOG 261, a randomized phase III trial of paclitaxel plus carboplatin versus ifosfamide plus paclitaxel in chemotherapy-naïve patients with newly diagnosed stage I–IV, persistent or recurrent carcinosarcoma or the uterus, fallopian tube, peritoneum or ovary.

Recurrence remains a significant problem in patients with early-stage uterine carcinosarcoma treated with chemotherapy alone (or in combination with radiotherapy), and more effective treatments are required to reduce the rates of local and distant failures.

Multimodality Therapy

It is evident that recurrence rates are high in uterine carcinosarcomas treated with adjuvant single-modality therapy (either chemotherapy or radiation). This has prompted several investigators to explore combination therapy with radiation and chemotherapy to address local and distant recurrences. Currently, there are no prospective trials open for multimodality therapy in uterine carcinosarcomas, thus, treatment benefit must be extrapolated from small numbers of patients evaluated retrospectively. Table 7 summarizes DFS and OS in patients with uterine carcinosarcoma treated with multimodality therapy.

Kohorn et al. found that four of five (80 %) patients treated with radiation, surgery, and adjuvant chemotherapy (doxorubicin/cyclophosphamide or doxorubicin/ cisplatin) were disease free after a follow-up of 36–60 months [123]. Manolitsas et al. examined outcome in 38 clinical stage I or II (lymphadenectomy not required) patients with uterine carcinosarcoma that received primary surgery followed by pelvic radiation and combination chemotherapy with four to six cycles of cisplatin (75 mg/m^2) and epirubicin (75 mg/m^2). Nine of 38 patients (24 %) were upstaged at the time of surgery. Chemoradiation was administered in a sequential or "sandwich" fashion with two cycles of chemotherapy given prior to pelvic radiotherapy, followed by completion of the chemotherapy. Patients were treated with WPRT unless a complete lymphadenectomy was performed and lymph nodes were documented to be negative. Those patients received vaginal brachytherapy only. Eleven patients (29 %) received no chemotherapy. Only one patient experienced grade 3 toxicity. Impressively, survival for patients who completed multimodality therapy was 95 % (20 of 21 patients) and DFS was 90 % with a median follow-up of 55 months. In contrast, OS among patients who did not receive the recommended treatment protocol was 47 %. There was one death (and one recurrence)

Table 7 Uterine carcinosarcoma: multimodality therapy

Reference	*N*	Modalities	DFS (%)	OS (%)
Kohorn et al. [123]	5	Surgery/RT/Chemotherapy[a]	80	
Manolitsas et al. [124]	21	Surgery/WPRT/cisplatin, epirubicin	90	95
Menczer et al. [125]	10	Surgery/cisplatin, Ifosfamide/WPRT	70	75[b]

RT radiation therapy, *WPRT* whole pelvic radiotherapy
[a]Chemotherapy consisted of doxorubicin/cyclophosphamide or doxorubicin/cisplatin
[b]OS for patients treated with WPRT alone = 50 % and 22 % for chemotherapy alone

among the 21 patients who received combination therapy. This patient experienced local and distant failure and was originally staged as IA (disease confined to a polyp) [124]. A recent study has reviewed all stages of uterine carcinosarcoma treated with chemotherapy alone, WPRT alone, or combined modality (chemotherapy followed by radiation). Out of 49 patients, 25 had clinical stage I tumors. Radiation was delivered as WPRT with HDR brachytherapy. Patients were treated with cisplatin and ifosfamide combination therapy as a single modality and in combination with radiation. Patients who received sequential therapy were administered a higher dose of cisplatin (80 mg/m^2 vs. 60 mg/m^2) and a lower dose of ifosfamide (1.2 g/m^2/day vs. 1.5 g/m^2/day). Ten patients received combined modality therapy with a 75 % 5-year OS compared to that of WPRT alone (50.5 %) and chemotherapy alone (22.2 %). Although sites of failure were not explicitly addressed in this study, multi-site failure (both pelvic and distant) appeared to be most common [125].

Summary

Uterine carcinosarcoma is a particularly aggressive neoplasm with high rates of treatment failure even when disease is confined to the uterus [86]. Molecular evidence points toward a clonal epithelial origin of these malignancies [81–85] and some evidence suggests more aggressive behavior if the epithelial component consists of serous carcinoma [95, 111]. However, both hematogenous and lymphatic spread have been described [86, 87]. Radiation appears to offer local control [108, 109], but distant failure remains problematic. Results from GOG 150 (whole abdominal radiotherapy vs. combination chemotherapy with cisplatin and ifosfamide), showed that there was no advantage of one over the other [99]. The most active chemotherapeutic regimen to date is ifosfamide plus paclitaxel and due to its toxicity now serves as the control arm in GOG 261 which is comparing ifosfamide plus paclitaxel with carboplatin and paclitaxel [120].

Conclusions

- Serous carcinoma, carcinosarcoma, clear cell carcinoma, and mixed histology tumors, although representing 5–10 % of all endometrial cancers, are responsible for a significant percentage of endometrial cancer mortality.
- These tumors are understudied in randomized-controlled trials and available retrospective data are limited by nonstandardized surgical staging and variable treatment regimens applied.
- As significant risk of disease spread outside the uterus exists, comprehensive surgical staging is of paramount importance.
- High local and distant failure rates in patients with early-stage disease have prompted testing of combined modality therapy with chemotherapy and localized radiation, utilizing both high-dose rate brachytherapy to the vaginal cuff or IMRT to the pelvis.
- While multimodality treatment is preferred in USC, clear cell, and mixed histologies, chemotherapy with ifosfamide and paclitaxel has proven most efficacious in carcinosarcoma.

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