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Non-Metastatic Uterine Carcinosarcoma: A Tailored Approach or One Size Fits All?

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Simple Summary: Carcinosarcoma of the uterus is a rare but aggressive disease. There is uncertainty regarding the optimal treatment regimen for early-stage disease, and the sequencing of chemotherapy and pelvic radiotherapy for advanced disease. This institutional review reports the outcomes of patients with carcinosarcoma and discusses management strategies.

Abstract: Purpose: Uterine carcinosarcomas are highly aggressive tumors of the endometrium and are associated with a poor prognosis. The optimal adjuvant treatment for both early and advanced-stage patients remains unclear. Methods: Cases of uterine carcinosarcoma were identified in our institution's pathology database between 2000 and 2022. Kaplan–Meier estimates were calculated for the local and distant recurrence-free, disease-free and overall survival; hazard ratios were calculated using Cox proportional hazards modelling for independent prognostic factors including the stage and treatment. Results: A total of 48 patients were identified as having uterine carcinosarcoma, of whom 70.8% were surgically staged. In total, 43 patients had pelvic-confined disease, while five had positive omental or peritoneal biopsies at surgery. There were 10 pelvic (20.8%) and 19 (39.6%) distant recurrences. None of the patients with stage IA disease who received chemotherapy and brachytherapy experienced disease recurrence. The local recurrence-free survival was 54.95%, the distant recurrence-free survival was 44.7%, and the overall survival was 59.6% at 5 years. Local recurrence-free survival and overall survival were inversely associated with advanced-stage OR 1.23 ($p = 0.005$) and OR 1.28 ($p = 0.017$), respectively, and no chemotherapy was associated with OR 1.96 ($p = 0.06$) and OR 2.08 ($p = 0.056$), respectively. Conclusion: The local and distant recurrence rates were high for advanced=stage patients even when treated with aggressive adjuvant therapy regimens. Chemotherapy may improve recurrence and survival. Early-stage patients may perform well with vaginal vault brachytherapy and chemotherapy. Further prospective comparisons are required between sequential, sandwich, and concurrent approaches to chemotherapy and radiotherapy, to optimize outcomes in this high-risk population.

Keywords: uterine carcinosarcoma; radiotherapy; chemotherapy

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1. Introduction

Uterine carcinosarcoma is a highly aggressive malignant tumor of the endometrium that is often associated with a poor prognosis [1,2]. These tumors are rare, and comprise both sarcomatous and epithelial components, likely owing to dedifferentiation and epithelial mesenchymal transition [1,3]. The type of carcinomatous component and the extent of the sarcomatous component, in addition to the stage, influence prognosis in individual cases. Uterine carcinosarcomas resemble metaplastic carcinomas, and most carry p53 mutations [1,3]. High rates of local and distant recurrences have been documented in the literature, even in early-stage patients. The definitive treatment for uterine carcinosarcoma

is a hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection; however, adjuvant chemotherapy and radiotherapy are recommended to mitigate the risk of recurrence [4].

The variability in the reported treatment regimens and outcomes in the literature demonstrates a lack of consensus for carcinosarcoma patients. Early-stage studies indicate that the 5-year survival for stage I uterine carcinosarcoma may be as low as 43% without adjuvant therapy [5]; however, other studies have reported that patients may perform well with only surveillance [2]. Balancing sufficient treatment with an avoidance of potential toxicities is therefore extremely challenging, and recurrences are generally fatal [3]. Patients with advanced-stage carcinosarcoma suffer poor outcomes even with combination chemotherapy and radiotherapy. Due to the rarity of this disease, the development of large prospective randomized trials has been challenging, and carcinosarcoma patients have been excluded from most advanced-stage adjuvant therapy trials in uterine cancer. We report the outcomes of a large cohort of carcinosarcoma patients receiving adjuvant treatment with chemotherapy and radiotherapy at our center.

2. Materials and Methods

All cases of uterine "carcinosarcoma" or "malignant mixed Mullerian tumor" in our institution's pathology database from 2000 to 2022 were identified. A gynecologic pathologist had reviewed all cases. Patients (i) with stage I-IIIC disease, as classified by the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging for uterine cancer (positive peritoneal or omental metastasis but no other distant metastatic disease allowed), (ii) with carcinosarcoma or the malignant mixed Mullerian tumor histologic subtype and (iii) who underwent a total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymph node staging were included. Pathologic diagnosis was based on the demonstration of a heterogenerous biphasic tumor composed of both epithelial (either endometrioid or non endometrioid subtype) and mesenchymal elements [1,3].

A retrospective chart review was conducted using the electronic medical record system (EMR). This project was approved by the local ethics board (REB project 15656). Patients were seen by a radiation oncologist, and either a gynecologic oncologist prescribing chemotherapy or a medical oncologist in a multi-disciplinary setting. In most cases, patients were also reviewed by a multi-disciplinary tumor board to review their pathology and discuss the optimal treatment regimen.

Statistical analysis was conducted using IBM SPSS Version 27. Descriptive statistics were used to present the patient, pathologic and treatment characteristics. The crude rates of local and distant recurrence and the proportion of patients surviving to the end of the study were reported. Kaplan–Meier analysis was conducted for local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), disease-free survival (DFS) and overall survival (OS). Cox proportional hazards ratios were used to assess the relationship between the stage and chemotherapy and LRFS, DRFS and OS. Hazard ratios with 95% CI were reported, with the alpha error set at $p = 0.05$ for significance.

3. Results

One hundred and eight patients with uterine carcinosarcoma were identified from the database. After exclusions for distant metastasis, insufficient data in (EMR), and patients who declined adjuvant therapy, 48 patients were included. The median age at diagnosis was 76.5 years (range 55–92). Thirty four patients were surgically staged with pelvic nodal dissections (70.8%). Of these, 10 had undergone sentinel lymph node assessments and 24 had undergone full dissections in the pelvis. Twenty (41.2%) patients had also undergone para-aortic lymph node assessment. The patient and pathologic data are displayed in Table 1.

Table 1. Patient disease and treatment characteristics.

PATIENT CHARACTERISTICS	
Patient Age	Median 76.5 (Range 55–92)
Stage IA IB II IIIA IIIB IIIC IV	N (%) 15 (31.3) 7 (14.6) 5 (10.4) 3 (6.3) 0 13 (27.0) 5 (10.4)
Characteristic Pelvic Nodal Dissection	N (%) 38 (79.2)
Median Pelvic Nodes Removed	10 (Range 0–23)
Para-Aortic Nodal Dissection Characteristic	19 (39.6) N (%)
Pelvic Nodal Dissection	38 (79.2)
Myometrial invasion none <50% >50%	 5 (10.4) 20 (41.7) 23 (48.0)
Lymphovascular Invasion Absent Present Unknown	 19 (39.5) 16 (33.3) 13 (27.0)
TREATMENT CHARACTERISTICS	
Concurrent Chemotherapy EBRT (PORTEC)	3 (6.3)
Sequential Chemotherapy and EBRT	9 (18.8)
Sandwich chemotherapy and EBRT	13 (27.0)
Chemotherapy Alone	14 (29.2)
EBRT Alone	5 (10.4)
Chemotherapy and VBT	4 (8.3)

EBRT = external beam radiotherapy, VBT = vaginal vault brachytherapy.

Overall, all but five patients received chemotherapy. Those five patents received external beam radiotherapy alone. Of the 43 patients who underwent chemotherapy, 14 had chemotherapy alone, 13 had sandwich chemotherapy and radiotherapy (three cycles of carboplatin paclitaxel and external beam radiotherapy, and three additional cycles of carboplatin paclitaxel), 9 had sequential chemotherapy then radiation, and 3 had concurrent chemoradiotherapy. Concurrent radiotherapy and chemotherapy were delivered using 5 weeks of pelvic radiotherapy (45–46 Gy in 23–25 fractions, plus or minus 11 Gy in 2 fractions for vaginal vault brachytherapy), with cisplatin delivered during weeks 1 and 4, and then carboplatin and paclitaxel delivered for four cycles every 3 weeks. The four patients who received vaginal vault brachytherapy and chemotherapy underwent a sandwich approach. See Table 2 for further details. The median overall adjuvant treatment time was 198 days (range 161–220).

Table 2. Treatment regimens by stage.

Stage	Concurrent Chemotherapy EBRT (PORTEC)	Sequential Chemotherapy and EBRT	Sandwich Chemotherapy and EBRT	Chemotherapy Alone	Chemotherapy and VBT	EBRT Alone
IA	1	1	2	5	3	3
IB	0	2	1	1	1	2
II	0	1	3	1	0	0
IIIA	0	0	2	1	0	0
IIIC	2	5	5	1	0	0
IV	0	0	0	5	0	0

EBRT = external beam radiotherapy, VBT = vaginal vault brachytherapy.

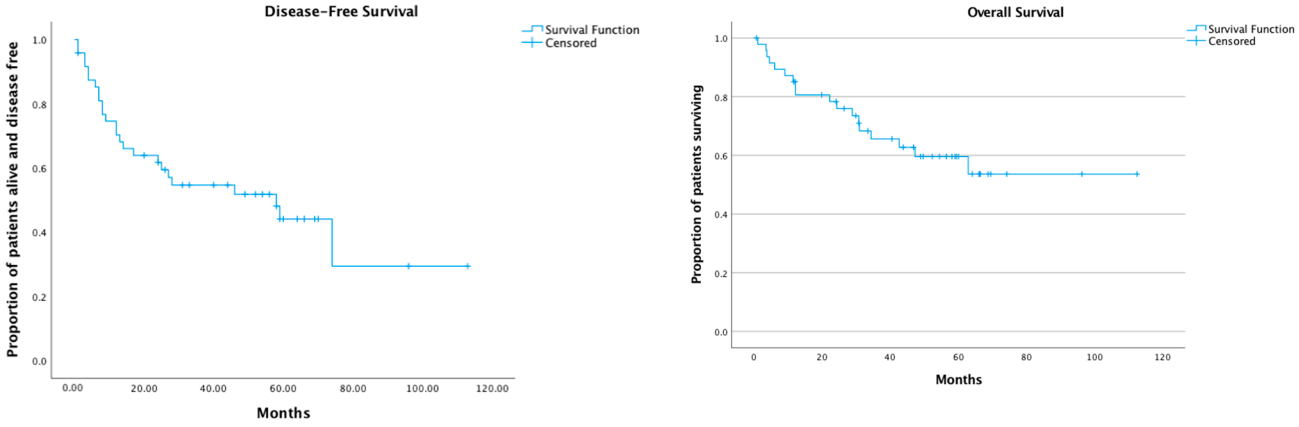
In the overall cohort, there were 10 pelvic (20.8%) and 19 (39.6%) distant recurrences, with five patients experiencing a local and distant recurrence. The median time to local recurrence was 32.0 months (range 0.66–438.5), and the median time to distant recurrence was 26.7 months (range 0.66–112.5). There were three isolated para-aortic nodal recurrences (6.25%) included in the distant recurrences. None of the patients who received chemotherapy and brachytherapy experienced disease recurrence; however, all had stage IA disease. At the study end, there were 23 patients alive with disease, 7 patients alive without disease, 17 patients had died of disease and 1 had died of another cause. Table 3 displays the characteristics of patients with recurrences.

Table 3. Characteristics and outcomes for patients with recurrence.

	Surgically Staged	Stage	Treatment	Recurrence Site	Salvage Therapy	Months Alive after Recurrence	Alive or Dead
1	Y	2		Pelvic sidewall, vaginal vault	Supportive Care		AWD
2	Y	3C	CT+EBRT	Distant lymph node	CT	3	DOD
3	Y	2	CT+EBRT+VBT	Distant lung	CT	16	DOD
4	Y	1B	CT+EBRT	PA, Distant lung	CT		AWD
5	Y	1A	CT	Pelvic sidewall, Distant abdomen		15	DOD
6	N		CT	Pelvic sidewall, Distant lung		4	DOD
7	Y	3C	CT+EBRT	Distant abdomen, lung	CT		AWD
8	N		CT	Pelvic sidewall	CT		AWD
9	Y	4	CT	Pelvic sidewall			DOD
10	Y	3C	CT	Distant lung		2	DOD
11	Y	4	CT	Distant abdomen	CT	14	DOD
12	Y	3C	CT + EBRT	PA	CT	27	DOD
13	Y	3A	CT + EBRT	PA	CT	13	DOD
14	Y	1A	EBRT	Pelvic		1	DOD
15	Y	3C	CT+EBRT+VBT	Distant abdomen		3	DOD
16	Y	3C	CT+EBRT+VBT	Distant lung			AND
17	Y	3C		Pelvic sidewall, Distant abdomen, lung	CT	4	DOD
18	Y	4	CT	Distant lung	Supportive care	5	DOD
19	Y	3C	RT/PORTEC	Pelvic sidewall	CT		AND
20	Y	3C	CT+EBRT+VBT	Distant-lung	Supportive care	14	DOD
21	Y	3C	RT/PORTEC+VBT	Pelvic, Distant lymph node		16	DOD
22	Y	3C	CT+EBRT	Pelvic sidewall, Distant lymph node	Supportive care		AWD
23	Y	1B	EBRT	PA	EBRT		AWD
24	Y	1A	CT	Distant abdomen, lung	CT	17	DOD

CT = chemotherapy, EBRT = pelvic external beam radiotherapy, VBT = vaginal vault brachytherapy, PA = para aortic, DOD = died of disease, AWD = alive with disease, AND = alive no disease.

The local recurrence-free survival was 79.1% at 1 year, 72.3% at 2 years, and 54.95% at 5 years. The median LRFS was 62.9 months (95% CI 30.1–95.4). The distant recurrence-free survival was 76.4% at 1 year, 63.3% at 2 years, and 44.7% at 5 years. The median DRFS was 58.1% (95% CI 14.7–101.5%). The disease-free survival was 76.7% at 1 year, 57.0% at 2 years, and 29.4% at 5 years, and the median DFS was 58 months (95% CI 20.1–95.9). The overall survival was 85.1% at 1 year, 78.3% at 2 years and 59.6% at 5 years. The DFS and OS survival curves are displayed in Figure 1a,b.



(**a**) (**b**)

Figure 1. (**a**) Disease-free survival and (**b**) overall survival.

On multivariable analysis, LRFS was inversely associated with advanced-stage disease (OR 1.23, p = 0.005), and was not significantly associated with nodal staging (OR 0.43, p = 0.9). There was a non-significant association between local recurrence and no chemotherapy (OR 1.96, p = 0.06). DRFS was inversely associated with advanced-stage disease (OR 1.25, p = 0.013), but was not associated with the treatment type (OR 1.40, p = 0.33) or nodal staging (OR = 1.42, p = 0.051). Overall survival was inversely associated with advanced-stage disease (OR 1.28, p = 0.017) and a lack of chemotherapy (OR 2.08, p = 0.056). OS was not associated with nodal staging (OR = 0.47, p = 0.17).

4. Discussion

Carcinosarcoma is a rare but aggressive histologic subtype of uterine cancer, with a high rate of recurrence and poor survival compared with traditional endometroid-type endometrial cancers [1–3]. The modest survival rate highlights the necessity of ensuring that these patients are adequately treated even when presenting with early-stage disease, yet there is currently a lack of consensus on the optimal adjuvant therapy regimen. The present study reports upon a large cohort of patients with uterine carcinosarcoma receiving a combination of adjuvant chemotherapy, pelvic radiotherapy, and vaginal vault brachytherapy. The predominant pattern of failure was distant, with 44.7% DRFS at 5 years. The majority of patients who experienced disease recurrence ultimately died of the disease, despite most receiving salvage chemotherapy, with a 5-year OS of 59.6%.

Given the rarity of this disease, most studies are retrospective and include small numbers of patients of variable stages, contributing to the difficulty in delineating the optimal treatment regimen for this patient group. Reed et al. demonstrated beneficial effects on pelvic recurrence in those patients receiving pelvic irradiation for carcinosarcoma compared with only observation [6]. Otsuki et al. performed a phase II single-arm trial of 51 patients who received 6 cycles of carboplatin and paclitaxel alone with a 78% completion rate. At 4 years, these rates were 67.9% (95% CI, 53.0–79.0%) and 76.0% (95% CI, 60.5–86.1%), respectively [7]. Einstein et al. more recently performed a large prospective study examining a sandwich regimen of three cycles of chemotherapy followed by whole pelvic

irradiation (45 Gy) and vaginal vault brachytherapy boost, with an additional three cycles of chemotherapy [4]. Patients with early-stage disease had excellent survival, with 84% at 3 years, and a median progression-free survival of 65.5 months. Advanced-stage patients had a 3-year overall survival of 50%, with a median PFS of 25.8 months. This regimen appears to have favorable outcomes and acceptable toxicity in comparison to previous regimens. Possible explanations for this include the earlier initiation of chemotherapy than some sequential regimens, a potential impact on the ability to complete treatments with the incorporation of a break from systemic therapy during radiation, or potential improved local control with earlier radiotherapy. Sequential regimens may still be considered on a case-by-case basis, and it is also unknown whether carcinosarcoma patients may benefit from concurrent chemotherapy and radiotherapy regimens.

The PORTEC 3 study has suggested that radiotherapy with concurrent and adjuvant chemotherapy is effective for stage IIIC patients, with an 11% failure-free survival benefit when adding chemotherapy [8]. Serous cancer patients in particular benefitted in terms of both failure-free survival (HR 0.42) and overall survival (HR 0.48) from the addition of chemotherapy to pelvic radiotherapy. Carcinosarcoma patients, however, were not included in this study. Similarly, other large studies on adjuvant therapy for advanced endometrial cancer have not represented carcinosarcomas well, including the prospective Italian trial [9], JGOG [10] and NSGO-EC-9501/EORTC-55991/MaNGO ILIADE-III [11].

The present study found that chemotherapy may be associated with improved outcomes in local RFS, distant RFS and overall survival, and should be considered in management decisions for the treatment of carcinosarcoma. The concurrent and sequential regimens have not been directly compared, and may be applied on a case-by-case basis depending on local and distant risk factors. Regardless, both chemotherapy and radiotherapy are generally recommended for advanced-stage disease due to the elevated risk of recurrence, despite the risk of toxicity.

There was a subset of patients in the present study with early-stage disease who received brachytherapy and chemotherapy, and did not experience local or distant recurrence. One retrospective study reported on 118 early-stage patients, 30% of whom did not receive adjuvant therapy [2]. In the multivariate analysis, adjuvant therapy was associated with improved vaginal recurrence, any recurrence, and overall survival. Of the patients who underwent only observation, 44% of the reported recurrences were in the vagina only, while those who received vault brachytherapy had a 2.3% rate of vaginal recurrence. Seagle et al. also reported a decreased risk of death with chemotherapy and vaginal brachytherapy in a retrospective study of stage 1 patients, compared with no treatment (HR (95% CI) 0.62 (0.54–0.73) and HR (95% CI) 0.83 (0.70–0.97), respectively) [12]. This warrants consideration as a recommendation during minimum vaginal vault brachytherapy in early-stage patients. A multi-disciplinary discussion should take place in early-stage cases to determine the optimal treatment based on patient and disease factors [13].

Recently, the molecular subtyping of endometrial cancers, including POLE, mismatch repair deficient (MMRd), no specific mutation profile (NSMP) and p53 abnormal have changed the landscape of adjuvant therapy for endometrial cancers as a whole [14,15]. The ongoing Transportec RAINBO trial is investigating the tailoring of therapy through all endometrial cancer stages based on molecular markers [16]. While the carcinosarcoma group was specifically excluded from prior studies, molecular profiling may still be applied in this group for early-stage patients. Approximately 70% of carcinosarcoma cases exhibit p53 mutations, while the percentage of POLE mutated cases varies in relation to the endometrioid component [17]. A recent study found that POLE mutated carcinosarcoma demonstrates improved outcomes that are similar to the endometrioid histology for POLE mutated cases, while those with p53 mutations have more aggressive disease than those with endometrioid p53 abnormal cases [18]. Therefore, the molecular subtype should be considered in carcinosarcoma patients, particularly in early-stage patients where the de-escalation of therapy can be considered [19].

There are also patients with carcinosarcoma in whom residual disease is present following surgery. The optimal treatment in this scenario is unknown. A retrospective review found inferior survival in carcinosarcoma patients with residual disease [20]. Radiotherapy, chemotherapy, and interstitial/intracavitary brachytherapy may be considered on a case-by-case basis in this scenario. The treatment sequence should also be tailored to the extent and location of the residual disease, as well as patient factors.

In those patients with recurrent or metastatic disease, prognosis is very poor, and the mainstay of treatment is systemic therapy. Tung et al. reported on 98 patients with recurrent disease after primary curative treatment, and found that only 7.6% of patients experienced survival after recurrence. Investigators reported that salvage therapy using radiotherapy (HR 0.27, 95% CI: 0.10–0.71), chemotherapy (HR 0.41, 95% CI: 0.24–0.72) or both (CRT) (HR 0.33, 95% CI: 0.15–0.75) is associated with improved survival after recurrence, though this may be influenced by the eligibility of patients to receive salvage therapy [3]. One meta-analysis found three trials overall, and two trials assessing the single agent ifosphamide compared with combination paclitaxel chemotherapy for advanced carcinosarcoma showed a lower risk of death and disease progression [21–24]. Of the 26 studies reporting on carboplatin and paclitaxel, tje progression-free survival was 5.9 months after first-line therapy, but only 1.8 months following subsequent lines [25]. A recent randomized trial examining the addition of pembrolizumab to standard chemotherapy versus chemotherapy alone in advanced uterine cancer found improved progression-free survival; however, carcinosarcoma patients were excluded from this trial [26]. The MITO 26 study demonstrated a modest benefit with trabectedin in patients with uterine or ovarian carcinosarcomas who had received at least two lines of systemic therapy for progressive metastatic disease, with 31% (90% CI: 20–44) of patients experiencing disease stabilization for a median of 2 months (95% CI: 1.78–2.30) [27]. Another study found minimal to no activity in carcinosarcoma patients receiving sorafenib [28]. Ongoing trials are investigating the use of pembrolizumab and Lenvatinib (NCT05147558) in uterine and ovarian carcinosarcoma [29]. Advances in precision medicine for targeting patients with certain molecular profiles with immunotherapy may also be relevant. Supportive care and symptomatic management should also be introduced early, given the poor prognosis of this disease and its propensity to progress quickly [17,30].

The limitations of this study include the small patient group and its retrospective nature. A proportion of patients were not surgically staged in the present study, and while not associated with adverse therapeutic outcomes during multivariable analysis, there is likely implications for the overall staging and treatment in patients with suboptimal nodal staging. Additionally, there was a very small number of patients who received concurrent chemotherapy and radiotherapy (5 weeks of pelvic radiotherapy (45–46 Gy in 23–25 fractions), with concurrent cisplatin delivered during weeks 1 and 4, and additional carboplatin and paclitaxel given every 3 weeks. This precludes a direct comparison with the sandwich and sequential combination treatments. There were also very few patients who received radiotherapy alone. Additional analyses could be conducted once a larger number of patients have received concurrent therapy, and further prospective and randomized studies should be pursued.

5. Conclusions

The local and distant recurrence rates were high for advanced-stage patients even when treated with aggressive adjuvant therapy regimens. Chemotherapy may be associated with recurrence and survival. Early-stage patients may perform well with vaginal vault brachytherapy and chemotherapy. Further prospective comparisons between sequential, sandwich, and concurrent approaches to chemotherapy and radiotherapy are required, to optimize outcomes in this high-risk population.

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Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: None of the authors of this paper have conflicts of interest to report.

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