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Outcomes of Adjuvant Radiation Therapy and Chemotherapy in Uterine Carcinosarcoma

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Abstract

To assess the impact on survival of adjuvant radiation therapy and chemotherapy in women with uterine Carcinosarcoma, a total of 44 patients were included in the cohort. Stages III-IV accounted for 20.5% and 43.2% respectively. Radiotherapy was delivered in 15 cases (34.1%) and chemotherapy was administered in 18.2% women with advanced stages. After a median follow up of 24.2 months, the 2-year progression free survival was 58.8% and the 2-year overall survival was 52.3%. In subgroups analysis, postoperative radiotherapy was associated with a better overall survival (HR, 4.02; 95% CI, 1.09-14.75; p=0.036). The combination of external beam pelvic radiation and vaginal brachytherapy improved significantly progression free survival ((HR, 0.28; 95% CI, 0.085-0.95; p=0.042). Systemic therapy did not show any survival benefit. The present study emphasizes the efficacy of radiation therapy in terms of progression free survival and overall survival. The role of chemotherapy warrants further investigations.

Keywords: Carcinosarcoma; Uterine cancer; Radiation therapy; Chemotherapy

Introduction

Uterine Carcinosarcomas (UCSs) account for only 2% to 3% of uterine cancers [1]. However, these tumors are responsible for more than 15% of uterine cancer associated deaths and have an overall survival rate of 30% to 40% [2]. Although the primary treatment for UCS is surgery, the high rates of both local and distant disease recurrence after surgery indicate the need for effective postoperative therapies. Radiotherapy alone or associated with chemotherapy seems to improve Progression Free Survival (PFS) and Overall Survival (OS) especially in advanced stages. The aim of this study was to determine survival outcomes and response to radiation therapy and chemotherapy in women with UCS.

Materials and Methods

Study design and patients

We performed a monocentric retrospective study that included women diagnosed with UCS between 1998 and 2013 at Salah Azaiez anti-cancer Institute, Tunisia. The hospital records of all patients were reviewed. Patient characteristics consisted of age, performance status, parity, menopausal status and medical history. Clinicopathologic information regarding histological diagnosis (epithelial and sarcomatous components), depth of myometrial invasion, pelvic washing cytology, and extra uterine spread of the disease to the parametrium, ovary, peritoneum, or distant organs were obtained. All patients were reclassified based on the 2009 FIGO staging guidelines. The sarcomatous component was subdivided into homologous or heterologous tumors. Surgical data included the surgical modality and the performance or not of pelvic and/or para-aortic lymphadenectomy. Postsurgical treatment was recorded as observation, radiation therapy (whole pelvic radiotherapy and/or brachytherapy), chemotherapy, or chemoradiotherapy. Adverse events were analyzed among different radiation and chemotherapy regimens and graded according to Common Terminology Criteria for Adverse Events (CTCAE v 4.0).

Statistical methodology

Overall survival, the time in months from diagnosis to death from any cause, and PFS, the time in months from diagnosis to death directly caused by the primary malignant tumor were defined as the primary outcomes. The Kaplan-Meier method was used to calculate the OS and PFS rates and median survival time. The log-rank test was used to formally test the differences. Univariate and multivariate Cox proportional hazards regression was performed. Ap-value <0.05 was considered

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Table 1: Characteristics of the study population.

	N (Total=44)	%
Age (years)		
< 65	25	56.8
≥ 65	19	43.2
Menopausal status		
Premenopausal	4	9
Menopausal	38	91
Parity		
0-1	7	15.9
≥ 2	37	84.1
History of breast carcinoma		
Yes No	14 28	31.8 68.2
FIGO stage		
I	10	22.7
II	6	13.6
III	9	20.5
IV	19	43.2
Sarcomatoid component		
Homologous	11	25
Heterologous	26	59
Unknown	7	16
Myometrial invasion		
< 50%	12	27.3
≥ 50%	29	65.9
Unkown	3	6.8

statistically significant in comparison between groups. Statistical analyses were carried out using SPSS statistics software package version 21.0 (IBM Corporation, Armonk, NY).

Results

Patient characteristics

A total of 44 women met the study eligibility criteria. The demographic and clinicopathological features are displayed in Table 1. Median age at diagnosis was 64 years (range, 48-83 years). Fourteen women (31.8%) had a history of breast carcinoma and ten of them (22.7%) were treated with tamoxifen. Most patients presented with abnormal vaginal bleeding (65.9%) and pelvic pain (13.6%). Advanced stages accounted for 63.7%.

Therapeutic management

All but 6 patients (86.3%) underwent surgery. Pelvic and para-aortic lymphadenectomy were performed respectively in 26 (59.1%) and 5 (11.4%) patients. Postoperative treatments according to stage are summarized in Table 2. Radiotherapy (external beam radiotherapy +/- brachytherapy) was delivered in 15 cases (34.1%). The median intented radiation dose was 45.5 Gray (range, 44-50 Gy). Grade 2 diarrheas and grade 1 cystitis was reported in 3 and 2 patients respectively. Chemotherapy was indicated for 8 women (18.2%) with advanced stages at diagnosis. Different regimens were administered as shown in Table 2. The median number of cycles was 5 (range, 2-6 cycles). Adverse events included grade 2 renal toxicity (n=3), grade 3 neutropenia (n=1) and grade 1 diarrhea (n=1). No toxicity related death was reported.

Table 2: Patterns of treatment by FIGO stage.

	Stages I-II (Total=16)		Stages III-IV (Total= 28)	
	N	%	N	%
RT and/or CT				
Yes No	7 9	43.7 56.3	10 18	35.7 64.3
Radiotherapy	7	43.7	8	28.6
External beam pelvic radiation	2	12.5	4	14.3
EBPR+ Vaginal brachytherapy	5	31.2	4	14.3
None	9	56.3	20	71.4
Chemotherapy	-	-	8	28.6
Paclitaxel/Carboplatin	-	-	3	10.7
Ifosfamide based regimen	-	-	4	14.3
Doxorubicin/Cyclophosphamide /Cisplatin	-	-	1	3.6
None	16	100	20	71.4

Abbreviations: RT: Radiotherapy; CT: Chemotherapy; EBPR: External Beam Pelvic Radiation

Table 3: Kaplan Meier analysis of PFS according to adjuvant treatment and FIGO stage.

	Stages I-II		Stages III-IV	
	Median PFS, (months)	95% CI	Median PFS, (months)	95% CI
Radiotherapy				
Yes	51.93	18.28-85.59	60.10	54.07-66.14
No	39.18	16.44-61.91	11.94	5.40-18.47
Chemotherapy				
Yes	-	-	48.06	21.82-74.30
No	55.27	30.24-80.29	40.03	4.47-75.60

Survival outcomes

Twelve patients (27.2%) out of 25 (56.8%) with complete remission status at the end-of-treatment, developed locoregional failure within a median time to relapse of 11.9 months (range, 4.8-55.7 months). Lung metastasis at relapse was also reported in 4 (9%) cases. After a median follow up of 24.2 months, the 2-year PFS was 58.8% and the 2-year OS was 52.3%. Patients who received a postoperative treatment had a tendency of better PFS (2-year PFS, 70% *vs.* 42.9%; p=0.39) and OS (2-year OS, 61.4% *vs.* 52.4%; p=0.23) although statistically non significant. The impact on PFS of each radiation therapy and chemotherapy by FIGO stage is shown in Table 3. Univariate analysis of the entire cohort revealed that radiotherapy (HR, 4.02; 95% CI, 1.09-14.75; p=0,036) was a predictor of OS and the combination of external beam pelvic radiation and vaginal brachytherapy improved significantly PFS (HR, 0.28; 95% CI, 0.085-0.95; p=0.042). The administration of chemotherapy was not associated with better outcomes. There was no statistically significant difference between subgroup in multivariate Cox regression analysis.

Discussion

The end point of this study was to assess the impact of RT and chemotherapy on survival in women with UCS. This retrospective cohort, as a whole, experienced a significant benefit in overall survival with postoperative radiation. Further analysis revealed that the combination of External Beam Radiotherapy (EBPR) plus Vaginal Brachytherapy (VB) predicted for improved progression-free survival.

Table 4: Univariate analysis of patterns of postoperative therapy affecting OS and PFS.

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
RT and/or CT *vs.* none	1.99	0.63-6.32	0.23	1.82	0.44-7.45	0.40
RT	4.02	1.09-14.75	0.036	1.82	0.44-7.45	0.40
EBPR+VB *vs.* EBPR	0.72	0.21-2.43	0.60	0.28	0.085-0.95	0.042
CT	0.62	0.22-2.43	0.74	1.80	0.22-14.75	0.58

Abbreviations: RT: Radiotherapy; CT: Chemotherapy; EBPR: External Beam Pelvic Radiation; VB: Vaginal Brachytherapy

These findings are consistent with the results of the SEER data-based study. In fact, of the 2461 women with UCS in the analysis, patients receiving radiotherapy with stages I-III disease experienced a benefit in overall survival compared to those who did not (HR,0.87; p=0.03). Women with stage IV disease experienced benefits in overall (HR, 0.63; P<0.001) and uterine-specific survival (HR, 0.63; p=0.004) with RT [3]. Two randomized trials have addressed the use of adjuvant RT in UCS: In the Gynaecologic Oncology Group (GOG-150) phase III trial, 232 patients with stage I-IV UCS were randomised to receive as postoperative therapy either Whole Abdominal Irradiation (WAI) of 30Gy followed by pelvic boost or cisplatin-ifosfamide and mesna. No statistically significant advantage in recurrence rate or survival was found between the two groups [4]. The second randomized trial of the European Organisation for Research and Treatment of Cancer (EORTC), including 91 patients with stages I-II UCS, did not show any difference in both OS and DFS between adjuvant pelvic RT and observation [5]. Although the contradictory results of survival benefit associated with RT, a marked decrease in the locoregional failure rate was observed in patients with UCS, with local recurrence rates of 47% and 24% in the observation *vs.* adjuvant RT respectively [6]. Sampath and Gaffney analyzed the role of adjuvant RT in all histologic types of uterine sarcoma and suggested that adjuvant RT reduced the local failure rate by 50% among cases of UCS, leiomyosarcoma, and endometrial stromal sarcom [7]. However, the optimal radio therapeutic modality (VB and/or EBPR) is not established (Table 4). Our study demonstrated that both EBPR and VB improved progression-free-survival. Whether the combination together may further improve vaginal and pelvic control is not known [8]. Data supporting chemotherapy are controversial as well. The small number of patients receiving chemotherapy in our cohort decreased the study's power to detect a statistically significant difference. In early-stage UCS, Garg et al. [9] performed a population-based analysis using the SEER Medicare database to evaluate the outcomes of adjuvant chemotherapy. There was statistically non-significant difference in median survival between patients treated with and without chemotherapy (Stage I: 54 months *vs.* 88 months, p=0.21; Stage II: 43 months *vs.* 30 months, p>0.05) [9]. Same findings were reported by Cantrell [10]. In advanced stages, several retrospective studies have assessed combining adjuvant RT and chemotherapy. Menczer et al. [11] analyzed 49 women with adjuvant treatment consisting of chemotherapy alone, RT alone or sequential chemotherapy and RT. Sequential chemotherapy and RT group experienced a significant improvement in five-year overall survival when compared to the chemotherapy only group and a non-significant benefit when compared to the RT only group [11]. An overall survival benefit was also found in the study reported by Wong [12,13]. In the GOG-150 trial, the adjuvant cisplatin-ifosfamide and mesna reduced recurrence rate and significantly prolonged overall survival in women with optimally debulked tumors [4]. Same chemotherapy regimen was evaluated by Sutton in a phase III trial and reported an improvement in response rate and progression free-survival in patients with advanced, persistent, or recurrent carcinosarcoma [14]. Further adjuvant phase III trial showed OS benefit of the combination ifosfamide and paclitaxel in patients with advanced uterine sarcoma with optimally debulked tumor and without extra-abdominal spread [15]. Paclitaxel and carboplatin, a relatively well tolerated regimen was reported to achieve high response rate in several phase II trials [16]. Hence, this regimen is commonly used as the first line option, pending the final results of the GOG 261, which compares ifosfamide and paclitaxel versus carboplatin and paclitaxel [17].

Conclusion

Uterine carcinosarcoma is an aggressive malignancy which standard management consists of surgery. Considering the sum of this evidence, the impact of adjuvant therapies in the treatment of women with UCS appears to result in survival improvement. Our results revealed the potential benefits of radiation therapy. Limitations of this report include the small number of patients and its retrospective nature, which allows patient selection bias. Large multi-center trials including multimodality approach with surgery, radiotherapy and chemotherapy are needed to overcome the rarity and the poor prognosis of the disease.

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