

RESEARCH ARTICLE

Impact of Treatment Strategies on Local Control and Survival in Uterine Carcinosarcomas in Turkey

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Abstract

Background: The purpose of this study was to determine the clinical characteristics, patterns of recurrence and survival outcomes in patients with uterine carcinosarcomas treated in our institution. **Materials and Methods:** Records of 26 patients diagnosed between 2007 and 2011 with uterine carcinosarcoma were retrospectively evaluated for demographic features, tumor characteristics, treatment regimens and patient outcomes in terms of DFS and OS. **Results:** Median age was 61 (range 43-78). 10 patients (38%) had stage I disease at diagnosis, 3 (12%) had stage II, 4 (15%) had stage III and 9 (35%) had stage IV. Sixteen patients (62%) received chemotherapy with paclitaxel and carboplatin for 6 cycles. One patient underwent radiotherapy. Median follow up was 17 months. Sixteen patients relapsed and 13 died during follow up. Considering recurrence, 5 out of 16 patients had lung metastases, one had brain metastases and 9 had only intraabdominal recurrence. The 3 year DFS was 37% and the 3 year OS was 30%. **Conclusions:** Our data show that uterine carcinosarcomas tend to be at advanced stage at diagnosis and despite the use of chemotherapy, overall prognosis is poor. Surgery remains the mainstay of treatment. More effective adjuvant strategies are needed to reduce relapse and death rates.

Keywords: Uterine carcinosarcoma - treatment - survival - Turkey

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Introduction

Carcinosarcomas (also termed malignant mixed mesodermal tumors [MMMTs], sarcomatoid carcinomas, or malignant mixed mullerian tumors) are relatively rare gynecologic tumors that occur throughout the female genital tract, most commonly in the uterus. (Brown et al., 2004). Carcinosarcomas of the uterus represent less than 3% of uterine neoplasms with an estimated annual incidence of less than two per 100,000 women (Powell et al., 2010). Historically, carcinosarcomas display both epithelial and stromal differentiation. Furthermore, the sarcomatous component of this entity has been previously subdivided into homologous (e.g. leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma) versus heterologous (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, or liposarcoma) cell types. However, there is now convincing evidence that most uterine carcinosarcomas are monoclonal neoplasms and are in reality metaplastic carcinomas. The sarcomatous component is derived from the carcinomatous element which is the driving

force (McCluggage, 2002). Therefore, the NCCN panel recently moved carcinosarcomas to the epithelial carcinoma guideline. Total abdominal hysterectomy and bilateral salpingo-oophorectomy represents the standard surgical treatment. Pelvic and/or para-aortic lymphadenectomy is indicated for carcinosarcoma. Carcinosarcoma also requires a comprehensive surgical peritoneal staging (Gaducci et al., 2007).

Significant progress in the treatment of advanced uterine carcinosarcoma was published in the last decade (Miller and King, 2008). GOG0108 previously showed that ifosfamide plus cisplatin offers a slight prolongation of progression-free survival but no significant overall survival benefit over ifosfamide alone in patients with advanced, persistent, or recurrent carcinosarcoma (Sutton et al., 2000). GOG0161 is the first randomized prospective trial in uterine carcinosarcoma that clearly demonstrates a superior overall survival for combination (ifosfamide and paclitaxel) chemotherapy compared to single agent treatment (ifosfamide) in the advanced setting (Homesley et al., 2007). On the other hand, data in the adjuvant treatment is more scarce. GOG0150 compared adjuvant

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ifosfamide and cisplatin to whole abdominal radiotherapy and found similar outcomes but a trend towards superior survival with chemotherapy (Wolfson et al., 2007). The role of radiotherapy after surgery has shown an increased local control with no significant effect on overall survival (Ferrer et al., 1999; Denschlag et al., 2007). Current guidelines recommend adjuvant chemotherapy in all stages and tumor directed RT in selected early stage cases.

Complete surgical staging with extensive lymph node dissection is routinely performed and adjuvant chemotherapy with paclitaxel and carboplatin is frequently utilized in patients with carcinosarcoma in our institution. Radiotherapy is rarely used in selected cases given the lack of survival benefit. Therefore our patients represent a unique group with complete surgical staging made by the same surgeon (A.A.) and adjuvant chemotherapy with paclitaxel and carboplatin utilized thereafter. The purpose of this study was to determine the clinical characteristics, patterns of recurrence and survival outcomes in patients with uterine carcinosarcoma treated in our institution.

Materials and Methods

Records of the patients with uterine carcinosarcoma were retrospectively evaluated and patients with carcinosarcoma diagnosed between 2007 and 2011 were identified. All patients were initially treated surgically by the same surgeon with comprehensive staging, i.e. total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymph node dissection and omentectomy. Chemotherapy regimen consisted of paclitaxel (175 mg/m²) and carboplatin (AUC 5-6) given every 21 days for 6 cycles. Demographic features, tumor characteristics, treatment regimens and patient outcomes in terms of disease free survival (DFS) and overall survival (OS) were analyzed.

Statistical analysis

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Kaplan–Meier

analysis was performed to examine OS or DFS. Disease free survival was defined as the time from primary surgery until recurrence of tumor or death from any cause. Overall survival was defined as the interval from primary surgery to the date of death or last follow-up. Statistical analysis was performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL) and statistical significance was set at P less than 0.05.

Results

Twenty six patients with carcinosarcoma who were operated between 2007 and 2011 in our institution were identified. Patient characteristics are shown in Table 1. Median age was 61 (range 43-78). Sixteen patients (62%) received paclitaxel and carboplatin regimen for 6 cycles. One patient received radiotherapy Median follow up was 17 months. Sixteen patients (63%) relapsed and 13 (50%) died on follow up. Considering the recurrences, 5 out of 16 patients had lung metastases, one had brain metastases and 9 had only intraabdominal recurrence. Two year DFS was 26% and 2 year OS was 48%.

Two year DFS (28% vs 23%, p=0.359) and OS (53% vs 49%, p=0.891) of patients with stage I-II disease and stage III-IV disease were similar.

Table 1. Patient Characteristics

	N	(%)
Age, median (range)	61	(43-78)
Comorbid diseases		
Hypertension	11	(42%)
Diabetes	8	(31%)
Coronary heart disease	7	(27%)
Chronic kidney disease	1	(4%)
Stage		
I	10	(38%)
II	3	(12%)
III	4	(15%)
IV	9	(35%)
Tumor size (cm)	6	(1.7-20)
Lymphovascular invasion	11	(42%)
Chemotherapy	16	(62%)
Radiotherapy	1	(4%)

Table 2. Results of Uterine Carcinosarcoma Observational Studies

Study	n	stage	LND	KT	RT	Recurrence%	DFS	OS
Makker 2008	38	1-4	OE 75%	+(60% PC, 20%IP)	+	50%	3 years PFS %35	3 years66%
	11			-	+	90%	3 years PFS 9%	34%
Bosquet 2010	121	1-4	LND 60%, without OE	25%+(MVAC, MAP,CAP)	38%		SI-II→5 years DFS 52%	5 years DSS 50%
							SIII→26% SIV→6%	
Einstein 2012	30	1-4	+	+(I±P)	+(sandwich)	17% S-II	NR	2 years80% SI-II
						70% SIII-IV		30% SIII-IV
Menczer 2005	49	1-4	+	IP	WAI		NR	5 years KT→22%
							NR	RT→ 50%
							NR	KT+RT→ 75%
								All group→ 60%
Sutton 2005	65	1-2	-	IP	-		2 years PFS 69%	2 years82 %
							NR	5 years62 %
							7 years54%	5 yil45%
GOG 150, 2007	105	1-4		IPx3	-	5 years52%	NR	5 yil45%
	101			-	WART	58%		35%
Wong, 2006	43	1-4		65% IP	65 % +		2 years PFS SI-II→80%	2 years 95% SI-II
							NR	25%SIII-IV
							SIII-IV→13%	
Kucukoztas 2012	26	1-4	+	62% PC	4%	61%	2 years26%	2 years48%

*RT:Radiotherapy, OS:overall survival, PFS:progression free survival, DFS:disease free survival, fu:follow up.OE:omentectomy, LND: lymphadenectomy, WAI:whole abdominal irradiation, DSS:disease specific survival, WART:whole abdominal radiotherapy, PC:paclitaxel-carboplatin, MVAC:metotrexate-vinblastin-adriamycin-cisplatin, MAP:metotrexate-adriamycin-cisplatin, CAP: cyclophosphamide-adriamycin-cisplatin, Sstage, IP: ifosfamide-cisplatin, NR:not reported

Discussion

Primary treatment of uterine carcinosarcoma is optimal cytoreductive surgery that has a positive effect on survival (Nemani et al., 2007). Previous studies suggest that cytoreductive surgery, with a goal of achieving a complete gross resection, is associated with an improvement in OS among patients with advanced uterine CS (Tanner et al., 2011). However, despite optimal cytoreductive surgery, >50% of patients with FIGO stage I-II disease will have recurrence. Therefore additional treatment modalities like radiotherapy or chemotherapy are needed to reduce recurrence and death rates.

Previously, chemotherapy was reserved for the treatment of recurrent and metastatic disease; it is now being used more frequently as adjuvant therapy for early stage disease (Arend et al., 2011). Ifosfamide is the most active single agent for carcinosarcoma. Ifosfamide±cisplatin yielded favorable results in the adjuvant setting whereas ifosfamide-paclitaxel regimen clearly demonstrated a superior overall survival in the advanced setting (Homesley et al., 2007). However, this treatment is inconvenient, costly and toxicity is considerable. Paclitaxel-carboplatin (PC) regimen is well-tolerated and easily delivered in outpatient clinics. It is commonly used in ovarian and endometrial cancer for many years. Data on the efficacy of PC regimen in uterine carcinosarcoma is limited. Among patients with advanced or recurrent disease, 54% response rate was achieved in a GOG study (Wolfson et al., 2007). Response rates were similar in another study and median PFS was 16 and 12 months in chemo naïve and previously treated patients, respectively (Hoskins et al., 2008). Makker et al showed superior efficacy with platinum based chemotherapy with or without RT over RT alone in patients with completely resected uterine carcinosarcoma. 60% of the patients had received paclitaxel plus carboplatin in this study (Makker et al., 2008). Ongoing studies are also assessing this regimen in adjuvant treatment of CS.

We also administered PC regimen in our patients. Two-year DFS was 26% and 2-year OS was 48% in our series. Outcomes in our series are relatively inferior when compared to other studies summarized in Table 2. Particularly the studies with combined modality protocols achieved lower recurrence rates and higher rates of DFS and/or OS. Ifosfamide “sandwiched” with RT was found to be an efficacious regimen for surgically staged CS patients with no residual disease, with 17% relapse rate and 80% 2-year OS in patients with stage I-II disease (Einstein et al., 2012). Bosquet et al reported 5-year DFS as 52% and 5-year disease specific survival as 50% with combined modality therapy in patients with stage I-II disease (Gonzalez et al., 2010). Two factors may account for the dissimilar outcomes in those studies and ours; First, all patients were completely surgically staged with omentectomy and pelvic/paraortic lymph node dissection in our series. Therefore adjuvant radiotherapy was not used. Previous studies suggest that radiotherapy offers a significant reduction in local recurrence rates (Reed et al., 2008) but the effect on survival is controversial. No survival advantage was seen in single studies but a SEER

analysis demonstrated statistically significant reduction in the risk of death in patients with stage I-III disease (Clayton et al., 2008). Possibly adjuvant radiotherapy might further improve outcomes in patients treated with chemotherapy, i.e. efficacy of RT on local control and possible effect on overall survival may be more apparent when chemotherapy controls/reduces distant disease.

Second, we used the PC regimen as adjuvant chemotherapy. Outcomes in the advanced setting are similar with PC compared with ifosfamide based regimens; however data is limited with PC regimen in the adjuvant setting (Toyoshima et al., 2004). Interestingly, in another trial which used adjuvant PC plus radiotherapy in 60% of the patients, 3 year PFS was also lower than that reported in the literature (35%) (Makker et al., 2008). On the other hand, a GOG study evaluated adjuvant ifosfamide-cisplatin in completely resected stage I-II carcinosarcoma patients and at 2 years, 69% were progression free and 82% remained alive (Sutton et al., 2005). Menczer et al reported 75% 5-year survival with ifosfamide-based adjuvant chemotherapy plus radiotherapy (Menczer et al., 2005). Although comparison of outcomes in different trials is inherently biased, low numbers of patients in individual trials or series make it impossible to refine the effect of all the confounding factors and draw definite conclusions. Knowing this, we can hypothesize that chemotherapy regimen may also account for a part of the difference.

Our data show that uterine carcinosarcomas tend to be more at more advanced stage at diagnosis. Despite optimal surgery and use of adjuvant chemotherapy, overall prognosis is poor. Surgery remains the mainstay of treatment. Multimodal adjuvant treatment that includes chemotherapy and radiotherapy can be the best available approach. More effective adjuvant strategies are needed to reduce relapse and death rates. Further studies are needed to define the best adjuvant chemotherapy regimen and to test the efficacy of radiotherapy in combination with chemotherapy in the adjuvant setting in uterine carcinosarcoma.

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