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Menopausal Status at Diagnosis is a Prognostic Indicator in Patients who are Operated for Uterine Carcinosarcoma

Rezeksiyon Edilmiş Uterin Karsinosarkom Tanılı Hastalarda Prognostik Bir Gösterge Olarak Tanı Anındaki Menopozal Durum

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Abstract

Objectives: Uterine carcinosarcoma is a rare type of uterine cancer, and due to its rarity, there is limited evidence for prognostic factors and treatment. The objective of this study is to assess the influence of histologic, clinical, and demographic characteristics on overall survival (OS) and recurrence-free survival (RFS).

Materials and Methods: Patients who had diagnosis of uterine carcinosarcoma and followed by the medical oncology department of three hospitals from Türkiye between January 2013 and January 2023 were retrospectively evaluated. All patients had local disease and were surgically managed, and patients were excluded if they did not have primary surgical management.

Results: The study included 62 women who were primarily treated with surgery and had a median age of 64.5 (interquartile range=14) years. Recurrence was observed in 26 patients (41.9%), with a median RFS of 11.63 months [95% confidence interval (CI): 1.99-21.26]. A shorter RFS was observed in patients with myometrial invasion [hazard ratio (HR) 2.48, 95% CI 1.04-5.93, p=0.04], while postmenopausal diagnosis was a predictor for longer RFS (HR 0.02, 95% CI 0.004-0.14, p<0.001). The median OS was 43.17 months. Postmenopausal diagnosis was associated with prolonged OS (HR 0.003, 95% CI 0-0.45, p<0.001).

Conclusion: The results of our study show that being diagnosed before menopause is linked to a shorter RFS and OS in women with uterine carcinosarcoma who had surgery to treat local disease.

Keywords: Uterine carcinosarcoma, prognostic factor, menopausal status

Öz

Amaç: Uterin karsinosarkom, nadir görülen bir uterus kanser türüdür ve nadir olması nedeniyle prognostik faktörler ve tedavi konusunda sınırlı veri bulunmaktadır. Bu çalışmanın amacı, histolojik, klinik ve demografik özelliklerin genel sağkalım (OS) ve nükssüz sağkalım (RFS) üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Ocak 2013 ile Ocak 2023 tarihleri arasında Türkiye'deki üç hastanenin tıbbi onkoloji bölümünde takip edilen uterin karsinosarkom tanısı almış hastalar retrospektif olarak değerlendirildi. Tüm hastalar tanı anında lokal hastalığa sahipti ve cerrahi olarak tedavi edildi; tanı anında metastatik olan veya primer cerrahi yapılmayan hastalar çalışmaya dahil edilmedi.

Bulgular: Çalışmaya, primer olarak cerrahi tedavi uygulanmış 62 kadın dahil edildi ve hastaların ortanca yaşı 64,5 (çeyrekler arası aralık=14) yıldı. Nüks, 26 hastada (%41,9) gözlendi ve ortanca RFS süresi 11,63 ay [%95 güven aralığı (GA): 1,99-21,26] olarak bulundu. Miyometrial invazyonu

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kısalmış RFS ile ilişkili bulunurken [risk oranı (HR) 2,48; %95 GA 1,04-5,93, p=0,04], tanı anında postmenopozal olmak daha uzun bir RFS ile ilişkili bulundu (HR 0,02; %95 GA 0,004-0,14, p<0,001). Ortanca OS süresi 43,17 aydı. Postmenopozal tanı, uzamış OS ile ilişki bulundu (HR 0,003; %95 GA 0-0,45, p<0,001).

Sonuç: Bu çalışma lokal hastalık için cerrahi ile tedavi edilen karsinosarkom tanılı hastalarda premenopozal dönemde tanı almanın daha kısa RFS ve OS ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: Uterin karsinosarkom, prognostik faktör, menapoz durumu

Introduction

Uterine carcinosarcoma, also known as malignant mixed Müllerian tumor, is a rare form of gynecological malignancy, constituting less than 5% of all uterine neoplasms (1). Typically characterized by aggressive behavior, uterine carcinosarcoma is often associated with 15% of all uterine cancer deaths (2). Even in early-stage cases the rate of relapse exceeds 50% (3-5). The median overall survival (OS) rate is less than 2 years for patient with stage 3-4 disease, and the 5-year cancer specific survival rates are about 60%, 20% and 10% for women with stage 1/2, 3, and 4 disease in the e, respectively (6-9).

Endometrial carcinosarcoma is an atypical neoplasm distinguished by its biphasic composition, comprising mesenchymal and epithelial elements (1). Tumor behavior of uterine carcinosarcoma is mainly driven by the carcinomatous component of the disease, whereas endometrial carcinosarcomas exhibit a metastatic pattern that utilizes the lymphatic and intraperitoneal pathways, similar to epithelial tumors and epithelial component is more commonly observed in metastasis (1,10,11). The staging system for carcinosarcoma aligns with that of endometrial carcinoma and based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines. FIGO stage, tumor size, deep myometrial invasion (≥1/2), cervical involvement, parametrial involvement, lymphovascular invasion (LVI), lymph node involvement, presence of heterologous element affect survival (4,6,12-14).

Due to the rarity of the disease, there is limited evidence for the treatment. Currently, surgery is the mainstay of the treatment and followed by adjuvant chemotherapy and radiotherapy (RT). There is no clear consensus regarding the adjuvant treatment of the carcinosarcoma. Although adjuvant RT is associated with lower local recurrence rate, there is no OS gain with adjuvant RT (15,16). While adjuvant chemotherapy is generally recommended for resected stage I-IV uterine carcinosarcoma, there remains no clear consensus regarding its use in stage imperforate anus disease (17,18). Cochrane review of phase III trials revealed that paclitaxel and ifosfamide regimen and cisplatin, ifosfamide, and mesna regimens were associated with longer recurrence-free survival (RFS) and OS compared to ifosfamide alone or RT (19). Based on the findings from the Gynecologic Oncology Group (GOG)-232B and GOG-261 trials, which demonstrated non-inferiority, and a better toxicity profile compared to the ifosfamide/paclitaxel regimen, the carboplatin/paclitaxel regimen is recommended as the preferred first-line treatment (20,21).

This retrospective study aimed to identify factors influencing the prognosis in resected uterine carcinosarcoma. Its primary objective was to assess the impact of demographic, clinical, and histologic characteristics on RFS and OS.

Materials and Methods

This is as a retrospective observational study. Patients who had diagnosis of uterine carcinosarcoma and followed by the medical oncology department of three hospitals from Türkiye between January 2013 and January 2023 were included in the study. All patients had local disease and were surgically managed, and none received neoadjuvant chemotherapy. Patients were excluded if they did not have primary surgical management. Patients were included in survival analysis if they had any post-operative follow-up contact with medical oncology department. Clinicodemographic features, pathology results and the treatments if any, and recurrence and survival data of the patients were recorded retrospectively. Patients were staged according to the 2023 FIGO staging system for endometrial carcinoma. Staging groups were classified as early FIGO stage (I-II) and advanced FIGO stage (III-IV).

RFS was defined as the date from surgery to the date of first recurrence or in absence of recurrence, to the date of death. OS was calculated from the date of diagnosis to the date of death.

This study has been approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no.: İ06-385-23, date: 16.06.2023).

Statistics Analysis

We conducted all statistical analyses using the IBM SPSS Statistics 24.0 Statistical Package Program. We described continuous variables as medians [interquartile range (IQR)] and categorical variables as percentages. The chi-square test was used to compare categorical variables, and the Mann-Whitney U test/Student's t-test was used to compare continuous variables. Kaplan-Meier method and log-rank tests were conducted for survival analysis. We performed multivariate analyses using

variables that had a p-value of less than 0.20 in the univariate analyses. To perform multivariable analyses and calculate hazard ratios (HRs) with 95% confidence intervals (CIs), we conducted Cox regression analyses. P-values of <0.05 were considered significant.

Results

From January 2013 to January 2023, 62 patients who primarily treated with surgery were included the analysis. Median age was 64.5 and majority of patients were postmenopausal (n=54, 87.1%). Fifty-two (83.9%) patients presented with abnormal uterine bleeding while 7 (11.3%) patients had abdominal pain. Most performed surgery type was total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic lymph node dissection and omentectomy. 91.5% of surgeries provided negative surgical margins. Median tumor size was 5.5 (IQR=5.2) cm. Almost half of the patients (48.4) had LVI and 53.2 % had deep myometrial invasion (≥1/2). Thirty-two (51.6%) patients had FIGO stage I-II disease. Other patients' characteristics were given in Table 1. Half of the patients received any type of adjuvant RT, and 34 (54.8%) patients treated with adjuvant chemotherapy other than concurrent chemoradiotherapy. Most commonly utilized chemotherapy regimen was carboplatin and paclitaxel combination (n=23) and followed by ifosfamide, mesna and doxorubicine combination (n=7).

Median follow-up time was 26.4 months. Recurrence occurred in 26 (41.9%) patients and of these 26 recurrences, 6 patients (23.1%) presented with local recurrence only and 20 patients (76.9%) presented with recurrence outside the pelvis (with or without local recurrence) (Table 2). Only 3 of the 7 patients who underwent surgery for the recurrence had negative surgical margins. At recurrence, 19 (73.1%) out of 26 patients

Table 1: Clinicodemographic and pathologic features of the patients

		Number (n=62)
Age (median-IQR)		64.5 (14)
Menopausal status	Postmenopausal (%)	54 (87.1)
	Premenopausal (%)	8 (12.9)
Symptom	Abnormal uterine bleeding (%)	52 (83.9)
	Pain (%)	7 (11.3)
	Other (%)	3 (4.8)
Pathologic malignity diagnosis before surgery	Carcinosarcoma	27 (43.6)
	Undifferentiated tumor or different malignancy	17 (27.4)
	No malign pathology	18 (29)
Type of surgery	TAH + USO (%)	2 (3.2)
	TAH + BSO (%)	13 (21)
	TAH + BSO + PLND (%)	11 (17.7)
	TAH + BSO + PLND + omentectomy (%)	35 (56.5)
	TAH + BSO + omentectomy (%)	1 (1.6)
Negative surgical margin (%)		54 (91.5)
Tumor size (cm, median, IQR)		5.5 (5.2)
Lymphovascular invasion	Yes	30 (48.4)
	No	30 (48.4)
	Not known	2 (3.2)
Myometrial invasion	<1/2 (%)	25 (40.3)
	≥1/2 (%)	33 (53.2)
	Not known (%)	4 (6.5)
Cervical involvement (%)		21 (33.9)
Adnexal involvement (%)		12 (19.3)
Lymph node involvement (%)		19 (30.6)
Hormone receptor status	ER and PR negative (%)	3 (9.7)
	Only PR positive (%)	1 (3.2)
	ER and PR positive (%)	5 (16.1)
	Not known (%)	22 (71)

Table 1: Continued		
		Number (n=62)
Grade	2 (%)	2 (3.2)
	3 (%)	15 (24.2)
	Not known (%)	45 (72.6)
FIGO stage	1-2 (%)	32 (51.6)
	3-4 (%)	30 (48.4)
Carcinoma type	Endometroid (%)	15 (24.2)
	Serous (%)	18 (29)
	Undifferentiated (%)	4 (6.5)
	Squamous differentiation (%)	5 (8.1)
	Not known (%)	20 (32.3)
Sarcoma type	Stromal sarcoma (%)	6 (9.7)
	Leiomyosarcoma (%)	11 (17.7)
	Undifferentiated stromal sarcoma (%)	11 (17.7)
	Rhabdomyosarcoma (%)	11 (17.7)
	Chondrosarcoma (%)	4 (6.5)
	Leiomyosarcoma + Rhabdomyosarcoma (%)	2 (4.3)
	Not known (%)	17 (27.4)
Adjuvant (chemo) radiotherapy (%)		31 (50)
Adjuvant chemotherapy (%)		34 (54.8)

BSO: Bilateral salpingo-oophorectomy, ER: Estrogen receptor, IQR: Interquartile range, PLND: Pelvic lymph node dissection, PR: Progesterone receptor, TAH: Total abdominal hysterectomy, USO: Unilateral salpingo-oophorectomy, FIGO: International Federation of Gynecology and Obstetrics guidelines

Table 2: Characteristics of recurrence		
		n=26
Initial FIGO stage	1-2 (%)	10 (38.5)
	3-4 (%)	16 (61.5)
Site of recurrence	Pelvis (%)	6 (23.1)
	Abdomen (%)	1 (3.8)
	Distant (%)	6 (23.1)
	Pelvis and abdomen (%)	5 (19.2)
	Pelvis and distant (%)	3 (11.5)
	Abdomen and distant (%)	5 (19.2)
Surgery for recurrence (%)		7 (26.9)
Chemotherapy (%)		19 (73.1)

FIGO: International Federation of Gynecology and Obstetrics guidelines

received chemotherapy, with the most commonly utilized regimens being carboplatin and paclitaxel (n=5), ifosfamide, mesna, and doxorubicin combination (n=5), and gemcitabine and docetaxel (n=3). Median RFS was 11.63 (95% CI 1.99-21.26) months (Figure 1A). In univariate analysis (Table 3), the presence of LVI (HR 2.11, 95% CI 1.01-4.31, p=0.04) and deep myometrial invasion (HR 3.14, 95% CI 1.34-7.34, p=0.008) were both associated with a shorter RFS (Tables 3, 4). Upon multivariate analysis, deep myometrial invasion was significantly associated with poorer RFS (HR 2.48, 95% CI 1.04-5.93, p=0.04) while postmenopausal diagnosis was a significant predictor for longer RFS (HR 0.02, 95% CI 0.004-0.14, p<0.001) (Figure 2A).

Median OS was 43.17 months (Figure 1B). Use of adjuvant chemotherapy was associated with poorer survival both in univariate and multivariate analysis (HR 2.76, 95% CI 1.09-6.96, p=0.03 and HR 5.74, 95% CI 1.87-17.36, p=0.002, respectively). In multivariate analysis, similar to RFS, postmenopausal diagnosis was associated with prolonged OS (HR 0.003, 95% CI 0-0.45, p<0.001) (Figure 2B, Table 2). Out of 32 patients who received adjuvant chemotherapy, 21 (65.6%) had FIGO stage III-IV disease. 61.1% of patients who received chemotherapy had serous carcinoma, whereas only 38.9% of patients in the no chemotherapy arm had serous carcinoma.

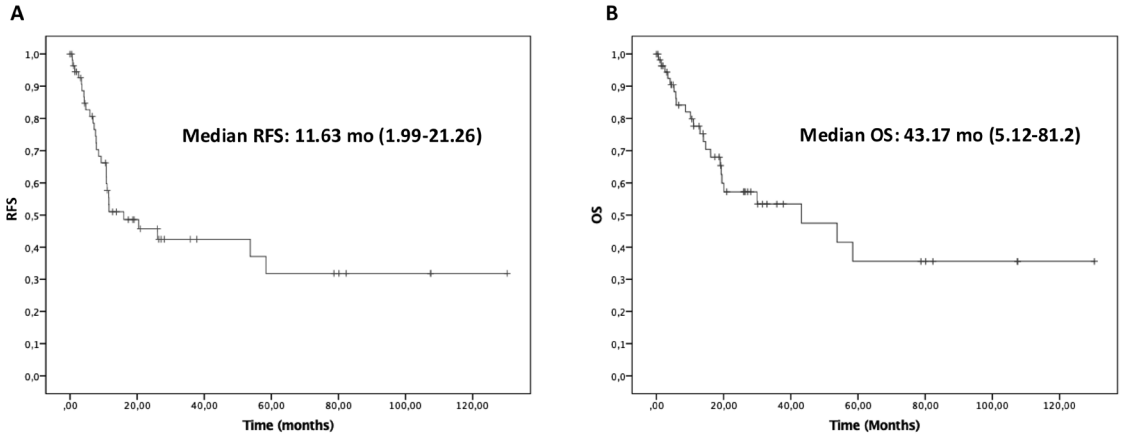

Figure 1: Recurrence free survival (A) and Overall survival (B)
OS: Overall survival, RFS: Recurrence-free survival

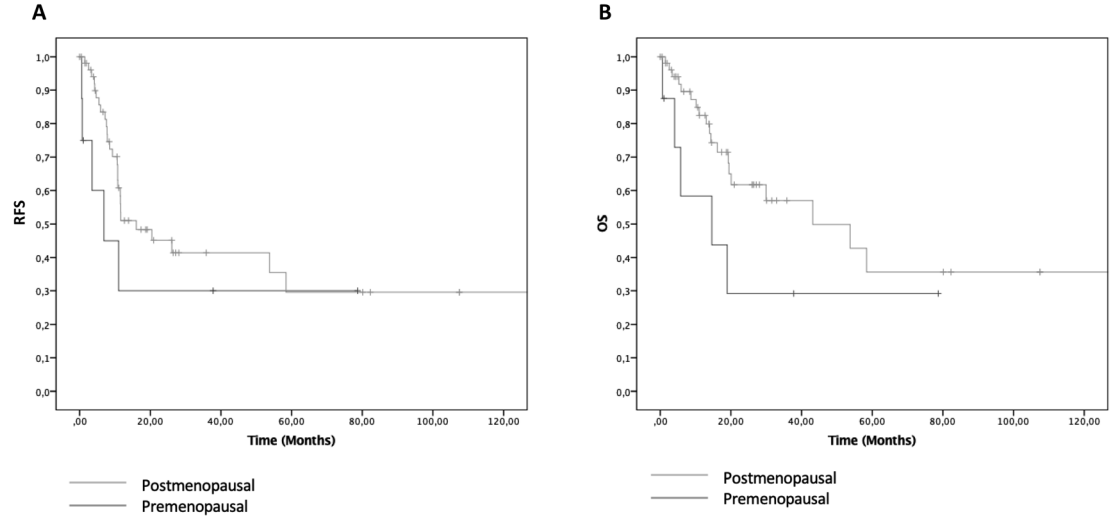

Figure 2: Recurrence free survival regarding menopausal status (A) and Overall survival regarding menopausal status (B)
OS: Overall survival, RFS: Recurrence-free survival

Table 3: Predictors of recurrence free survival

	Univariable analysis		Multivariable analysis, initial model		Multivariable analysis, final model	
Predictors	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65	0.80 (0.39-1.62)	0.54	0.60 (0.23-1.51)	0.27	-	
Menopausal status/ Postmenopausal	0.56 (0.21-1.47)	0.24	0.01 (0.002-0.13)	<0.001	0.02 (0.004-0.14)	**<0.001**
Lymphovascular invasion	2.11 (1.01-4.31)	0.04	1.94 (0.71-5.27)	0.19	-	
Deep myometrial invasion	3.14 (1.34-7.34)	0.008	2.70 (1.00-7.24)	0.04	2.48 (1.04-5.93)	**0.04**
Cervical invasion	1.82 (0.90-3.67)	0.09	0.64 (0.21-1.94)	0.43	-	
Adnexal invasion	1.41 (0.58-3.53)	0.42	0.60 (0.15-2.37)	0.46	-	
Lymph node positivity	1.93 (0.95-3.92)	0.06	1.00 (0.24-4.12)	0.99	-	
FIGO stage (I-II or III-IV)	1.57 (0.78-3.17)	0.20	0.97 (0.26-3.66)	0.97	-	
Adjuvant (chemo) radiotherapy (yes)	1.09 (0.53-2.22)	0.80	0.54 (0.22-1.32)	0.17	-	
Adjuvant chemotherapy (yes)	2.10 (0.97-4.52)	0.05	2.33 (0.90-6.00)	0.07	2.07 (0.88-4.82)	0.09

FIGO: International Federation of Gynecology and Obstetrics guidelines, CI: Confidence interval, HR: Hazard ratio

Table 4: Predictors of overall survival						
	Univariable analysis		Multivariable analysis, initial model		Multivariable analysis, final model	
Predictors	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age ≥65	0.77 (0.33-1.77)	0.53	0.38 (0.11-1.31)	0.12	-	
Menopausal status/ Postmenopausal	0.47 (0.17-1.26)	0.13	0.002 (0-0.06)	<0.001	0.003 (0-0.45)	**<0.001**
Lymphovascular invasion	1.50 (0.65-3.48)	0.33	1.55 (0.51-4.74)	0.43	-	
Deep myometrial invasion	2.13 (0.83-5.46)	0.11	1.70 (0.51-5.60)	0.38	-	
Cervical invasion	1.61 (0.71-3.64)	0.24	0.47 (0.11-2.06)	0.32	-	
Adnexal invasion	0.89 (0.26-3.04)	0.85	0.14 (0.01-1.58)	0.11	0.16 (0.02-1.26)	0.08
Lymph node positivity	1.62 (0.70-3.72)	0.25	0.86 (0.13-5.55)	0.87	-	
FIGO stage (I-II or III-IV)	1.16 (0.52-2.60)	0.70	1.03 (0.19-5.55)	0.97	-	
Adjuvant (chemo) radiotherapy (yes)	0.89 (0.39-2.02)	0.78	0.24 (0.06-0.86)	0.03	0.42 (0.16-1.10)	0.07
Adjuvant chemotherapy (yes)	2.76 (1.09-6.96)	0.03	7.89 (1.91-23.5)	0.002	5.74 (1.87-17.36)	**0.002**
FIGO: International Federation of Gynecology and Obstetrics guidelines, CI: Confidence interval, HR: Hazard ratio						

Discussion

Uterine carcinosarcoma is an uncommon condition, and the absence of a standardized therapeutic method hinders the conduction of studies on this cancer. We conducted a retrospective analysis of data from 62 patients who had local uterine carcinosarcoma and were treated with surgery. The study investigated the clinical features and pathological factors that impact RFS and OS. Carcinosarcomas are recognized as one of the most aggressive types of uterine tumors, characterized by a propensity for hematogenous spread, leading to poor OS outcomes. Peak incidence is observed in sixth and seventh decades (6). In our study, the median age at which patients were diagnosed was 64.5 years (IQR=14), with the majority (87.1%) being postmenopausal.

In our study, recurrence rate was 41.9% within 26.4 months of median follow-up time. Recurrence rate was reported within the range 27-82% in the literature (12,13,22-24). Differences between recurrence rates may be related to patients' characteristics, disease stage and the duration of the follow-up time. Median RFS was 11.63 (95% CI 1.99-21.26) months in our study. A Japanese study with similar patient characteristics regarding FIGO stage, deep myometrial invasion, and presence of LVI, but with a higher percentage (91%) of patients receiving adjuvant chemotherapy, reported a RFS of 16.4 months (25). But in that study, adjuvant chemotherapy did not show a significant impact on RFS (HR 1.93, 95% CI 0.55-6.74, p=0.30) (25). Relative these studies in the literature, underutilization of adjuvant therapy may be the cause of shorter RFS in our study. GOG-150 trial showed benefit of adjuvant chemotherapy over RT with 5 years recurrence rates of 58% vs. 52%, respectively (26). Although the supporting evidence is limited, adjuvant platinum-based chemotherapy has an impact on RFS, rather than RT, single-agent chemotherapy, or observation in patients with FIGO stage IB-IV carcinosarcoma. In our study, deep myometrial invasion was associated with shorter RFS while postmenopausal diagnosis was associated with prolonged RFS in multivariate analysis (HR 2.48, 95% CI 1.04-5.93, p=0.04 and HR 0.02, 95% CI 0.004-0.14, p<0.001, respectively). Previous studies showed that deep myometrial invasion alongside the larger tumor size, FIGO stage, presence of residual tumor, cervical invasion, adnexal involvement, nodal involvement, higher cancer antigen (CA)-125 levels, sarcoma dominance were associated with early recurrence in uterine carcinosarcoma (6,13,25,27,28).

Median OS was 43.17 months in our study and OS was longer in postmenopausal patients (HR 0.003, 95% CI 0-0.45, p<0.001). Although studies have shown varying results regarding the impact of age on recurrence and OS, the menopausal state has not been commonly evaluated in these studies (12,29). In a retrospective study, late onset of the menopause was associated with a lengthened OS (29). Estrogen receptors were expressed in 44% of patients with uterine carcinosarcoma, potentially indicating an association with better histological differentiation (30). Median OS for patients with hormone receptor positive carcinosarcoma was significantly longer than for patients with hormone receptor negative tumors (31). However, effect of patient's hormonal status on prognosis of carcinosarcoma is unknown. Additionally, almost all the patients in our study underwent BSO, so the OS advantage observed in postmenopausal women in our study can be attributed to the more aggressive tumor behavior rather than the effect of hormonal status in premenopausal women. Adjuvant chemotherapy was associated with poor survival in our study. While adjuvant chemotherapy

extends RFS, it does not have a beneficial effect on OS in also other studies (26,28,32). It may be due to the high proportion of serous carcinoma and FIGO stage III-IV disease in chemotherapy arm. Use of less effective regimens after adjuvan chemotherapy may be another cause.

Study Limitations

We acknowledge the various limitations of our study. Initially, the sample size in certain patient subgroups is very limited, hence restricting our capacity to carry out comprehensive subgroup analysis. Furthermore, because this study is retrospective, there is a lack of data regarding markers that may affect the prognosis, such as tumor grade, hormone receptor status, CA-125 levels. Lastly, the lack of standardized treatment protocols among patients can impact the results of the study. These constraints underscore the necessity of exercising prudence while interpreting and extrapolating the findings of the study. We need future research with larger, more comprehensive datasets and standardized protocols to address these limitations and provide more definitive conclusions.

Conclusion

In conclusion, due to the rarity of uterine carcinosarcoma, conducting prospective studies with large sample sizes is challenging. The information available in the literature on this cancer type is conflicting, and our understanding of prognostic factors and optimal adjuvant treatments remains limited, with several gray areas requiring clarification. Our study findings suggest that a premenopausal diagnosis is associated with shorter RFS and OS. A multidisciplinary approach is essential to improve survival outcomes and enhance the quality of life for patients with uterine carcinosarcoma.

Ethics

Ethics Committee Approval: This study has been approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no.: İ06-385-23, date: 16.06.2023).

Informed Consent: This is as a retrospective observational study.

Footnotes

Authorship Contributions

Concept: H.B., E.B.K., Design: H.B., E.B.K., Data Collection and/or Processing: H.B., M.Y., S.S., F.Y., O.A., D.U., O.Y., Analysis and/or Interpretation: H.B., M.Y., Literature Search: H.B., E.B.K., Writing: H.B., D.U., O.Y., E.B.K.

Conflict of Interest: There is no potential conflict of interest to declare.

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