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The prognostic significance of the heterologous component in uterine carcinosarcomas

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SUMMARY

OBJECTIVE: Uterine carcinosarcomas are aggressive, rare biphasic tumors with malignant epithelial and malignant sarcomatous components. The prognostic significance of the presence of extrauterine sarcoma (heterologous component) is controversial. Therefore, the aim of this study was to investigate the effect of heterologous components in uterine carcinosarcomas on disease-free survival, overall survival, and other prognostic factors.

METHODS: Clinical and histopathological data from patients treated for uterine carcinosarcoma in a tertiary cancer center in Turkey between July 2000 and January 2020 were collected. Independent risk factors affecting overall survival and disease-free survival were analyzed by univariate and multivariate Cox regression analyses.

RESULTS: A total of 98 patients were identified. The median follow-up was 21.8 (1.2–233.1) months. In the multivariate analysis, the median overall survival and disease-free survival were 23.8 and 20.7 months in those with homologous mesenchymal components and 17.6 and 9.7 months in those with heterologous mesenchymal components, respectively. It was found that the presence of heterologous mesenchymal components significantly reduced both overall survival and disease-free survival (odds ratio [OR], 2.861; 95% confidence interval [CI] 1.196–6.841; p=0.018 and OR, 3.697; 95%CI 1.572–8.695; p=0.003, respectively). In addition, both lymphadenectomy and adjuvant radiotherapy were found to significantly increase overall survival and disease-free survival. Age was found to increase only disease-free survival.

CONCLUSION: The results obtained in this study showed that the presence of heterologous components in uterine carcinosarcoma is a prognostic factor that adversely affects both overall survival and disease-free survival. Lymphadenectomy and adjuvant radiotherapy have beneficial effects on both overall survival and disease-free survival.

KEYWORDS: Uterine neoplasm. Cancer of uterus. Carcinosarcoma. Prognosis. Survival.

INTRODUCTION

Uterine carcinosarcomas (UCs), which are also known as malignant mixed mesenchymal tumors, are extremely aggressive and rare tumors[1]. Although carcinosarcomas account for only 5% of all uterine tumors, they are responsible for 15% of deaths due to uterine corpus malignancies[2]. UCs are biphasic tumors with malignant epithelial and sarcomatous components[3]. The sarcomatous component can be homologous (uterine-type mesenchymal tissue) or heterologous (non-gynecological mesenchymal tissue)[3].

UCs are classified as endometrial cancer, and surgical staging is performed according to the recommendations of the International Federation of Gynecology and Obstetrics (FIGO)[4]. The main treatments for UCs are total hysterectomy, bilateral salpingo-oophorectomy (BSO), systematic pelvic and paraaortic lymph node dissection (PPLND), omentectomy or omental biopsy, and resection of the entire gross mass[5]. Adjuvant therapy is indicated for patients in stages IB–IV and is closely associated with overall survival (OS)[6].

Various clinical features and prognostic factors that affect treatment response and determine prognosis have been evaluated in previous studies. Cancer stage, epithelial component grade, performance status, cancer antigen (CA) 125 level, lymphovascular site invasion (LVSI), depth of myometrial invasion, lymphadenectomy, lymph node metastasis (LNM), presence of residual tumor, and adjuvant therapy have all been associated

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with survival[6-10]. However, the prognostic effect of the heterologous component is controversial[2,3,5,11,12].

Therefore, the aim of this study was to investigate the effect of the heterologous component on disease-free survival (DFS) and OS in UCs and examine other clinical and histopathological features that affect prognosis.

METHODS

The records of patients treated for UC in the gynecological oncology clinic of a tertiary cancer center between July 2000 and January 2020 were reviewed. The files of 107 patients diagnosed with carcinosarcoma were reviewed. A total of 98 patients who underwent surgical staging in our clinic, whose paraffin blocks were evaluated by pathologists specializing in gynecological oncology, and who received adjuvant treatment in our hospital were included in the study. Four patients who underwent surgery at another center but received adjuvant treatment at our clinic were excluded from the study.

Patients' demographic characteristics, surgical and histopathological characteristics, and clinical results were retrieved from hospital records. Age at diagnosis, date of diagnosis, body mass index (BMI), CA 125 level, stage, tumor diameter, tumor grade, myometrial invasion, LVSI, cervical invasion, whether lymphadenectomy was performed, LNM, omental metastasis presence, histopathological features, presence of residual disease, adjuvant treatments, recurrence status, date of last follow-up, date of recurrence, and time of death were recorded.

Staging was carried out according to the FIGO 2009 staging system. Surgical staging included TAH, BSO, PPLND, total omentectomy, or omental biopsy. Optimal cytoreduction surgery was indicated for residual tumors of <1 cm, while suboptimal surgery was indicated for residual tumors of >1 cm. Among the histopathological features, epithelial and mesenchymal components were examined separately. The epithelial component was initially divided into two groups: endometroid and non-endometroid. Endometrioid types were classified histologically into grades 1, 2, and 3. In the non-endometroid group, cases were categorized as serous carcinoma, clear cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma, and serous+clear cell carcinoma. The mesenchymal component was classified as either homologous or heterologous. Homologous-type sarcomas include leiomyosarcoma, endometrial stromal sarcoma, and high-grade/undifferentiated sarcoma. Heterologous types included rhabdomyosarcoma, chondrosarcoma, osteosarcomas, and double or triple comorbidities.

The time from surgery to recurrence was used to calculate DFS. The time from surgery to the date of the last follow-up or death was used to calculate OS. The time from the date of first diagnosis to the date of the last follow-up or death was used to calculate the mean follow-up period. The study was performed in accordance with the World Medical Association Declaration of Helsinki, and ethical approval was obtained from the ethics committee of Tepecik Training and Research Hospital with decision number 2021/02-25.

Data were analyzed using IBM SPSS V23. Independent risk factors affecting OS and DFS were analyzed by univariate Cox regression analysis. The Kaplan-Meier test was used to compare the prognostic factors with OS duration. Categorical data were expressed as frequency and percentage, while quantitative data were presented as mean, standard deviation, median, minimum, and maximum. $p<0.05$ was considered statistically significant in all analyses.

RESULTS

A total of 98 patients were evaluated. The median age of the patients was 63 (45–84) years. The median follow-up was 21.8 (1.2–233.1) months. The median CA 125 level was 21.07 (2.98–3290). According to the histopathological features of the patients, 75 (76.5%) had LVSI. Deep myometrial invasion was detected in 69 (70.4%) patients, whereas cervical invasion was detected in 39 (39.8%) patients. Lymph node dissection was performed in 87 (88.8%) patients, and LNM was detected in 22 (22.4%) patients. Optimal cytoreductive surgery (residual tumor>1 cm) could not be performed in 18 patients (18.4%) because of their poor general condition or diffuse nonresectable tumor (Table 1).

Independent risk factors affecting OS and DFS were analyzed by univariate Cox regression analysis. Stage 4, presence of LVSI, cervical invasion, increased tumor diameter, increased CA 125 level, presence of LNM, lack of optimal cytoreduction (residual disease>1 cm), presence of non-endometrioid epithelial component, and lack of radiotherapy significantly reduced OS and DFS. While lymphadenectomy was associated with OS, it did not significantly affect DFS. The heterologous mesenchymal component was found to be associated only with DFS. Age, BMI, and adjuvant chemotherapy did not have a statistically significant effect on either OS or DFS (Table 2).

When the independent risk factors affecting OS and DFS were analyzed by multivariate Cox regression analysis (Table 2), median OS and DFS were found to be 23.8 (3.02–31.7) and 20.7 (3.0–231.7) months in those with a homologous mesenchymal component and 17.6 (1.2–233.1) and 9.7 (1.2–233.1) months in those with a heterologous mesenchymal component, respectively. The heterologous mesenchymal component had a

Table 1. Demographic and clinical characteristics of patients.

	%/Median (Range)
Age (years)	63 (45–4)
BMI	31.6 (20.7–51.4)
Average follow-up time (months)	21.8 (1.2–233.1)
CA 125	21.07 (2.98–3290)
Tumor diameter (cm)	6 (1–30)
Stage	
Stage 1	43.9
Stage 2	14.3
Stage 3	19.4
Stage 4	12.4
Lymphadenectomy	
Yes	88.8
No	11.2
Lymph node metastasis	
Yes	22.4
No	66.3
Residual disease (cm)	
>1	18.4
<1	81.6
Epithelial component	
Endometrioid type	45.9
Grade 1	2.0
Grade 2	23.5
Grade 3	20.4
Non-endometrioid	54.1
Serous carcinoma	44.9
Squamous cell carcinoma	4.1
Undifferentiated carcinoma	3.1
Clear cell carcinoma	1.0
Serous + clear cell carcinoma	1.0
Mesenchymal component	
Homologous	74.5
Endometrial stromal sarcoma	4.1
Leiomyosarcoma	14.3
High-grade/differentiated sarcoma	56.1
Heterologous	25.5
Rhabdomyosarcoma	13.3
Chondrosarcoma	8.2
Osteosarcoma	1.0
Rhabdomyosarcoma/ chondrosarcoma /osteosarcoma	2.1
Rhabdomyosarcoma/ chondrosarcoma	1.0

BMI (kg/m^2): body mass index; CA 125 (IU/mL): cancer antigen 125.

significant effect on both OS and DFS (Figure 1) (odds ratio [OR], 2.861; 95% confidence interval [CI] 1.196–6.841; p=0.018 and OR, 3.697; 95%CI 1.572–8.695; p=0.003, respectively).

DISCUSSION

Most UC cases have a single epithelial component, a poorly differentiated serous carcinoma. However, endometrioid, clear cell, mucinous, squamous, and undifferentiated histological types can all be observed. Similar to the epithelial component, the mesenchymal component often has a single sarcomatous component, with the most common homologous component being high-grade stromal sarcoma. Rhabdomyosarcoma is the most common heterologous component, followed by chondrosarcoma, osteosarcoma, and liposarcoma[1]. A consensus has emerged in UC regarding some prognostic factors such as stage, lymphadenectomy, residual disease, and adjuvant therapy that affect survival[6,10,12,13]. In this study, which was conducted in a tertiary reference center with more than 20 years of experience in the field of gynecological oncology, we found that the presence of a heterologous component in UC shortened both OS and DFS compared with the presence of a homologous component. Multivariate analysis showed that the heterologous mesenchymal component had a significant effect on both OS and DFS.

To the best of our knowledge, this is the first study to report that the heterologous component negatively affects both OS and DFS in all carcinosarcoma stages. Fergusson et al. evaluated only stage 1 patients and found that patients with heterologous components had worse DFS and 3-year OS[11].

In a multicenter retrospective study that accumulated the largest data in the United Kingdom, Marsoo et al. evaluated 1,192 patients[14]. The patients were divided into four groups. The 5-year progression-free survival (PFS) rate was 50.6% for low-grade/homologous, 50.6% for low-grade/heterologous, 45.8% for high-grade/homologous, and 34.0% for high-grade/heterologous cases. For low-grade carcinoma cases, the presence of heterologous components showed worse PFS but did not make a statistically significant difference. In high-grade carcinoma cases, the presence of heterologous components resulted in significantly worse outcomes.

Revirosa et al. investigated the pathological prognostic factors of 81 stage 1–3 patients, and the multivariate analyses revealed no significant results for age, heterologous components, or myometrial invasion, except for the disease stage[12]. Temkin et al. evaluated 47 patients and reported that the heterologous components did not affect either OS or DFS in stage 1–2 patients[10]. This result could be attributed to the inclusion

Table 2. Cox regression analysis results.

	Overall survival		Disease-free survival	
	OR (95%CI)	p	OR (95%CI)	p
Univariate				
Age	1.016 (0.981–1.052)	0.375	1.018 (0.983–1.054)	0.321
BMI	1.022 (0.968–1,090)	0.422	1.016 (0.964–1.071)	0.547
Stage (reference: Stage 1)				
Stage 2	0.776 (0.288–2.093)	0.617	0.755 (0.280–2.034)	0.578
Stage 3	0.977 (0.406–2.352)	0.959	1.054 (0.437–2.538)	0.907
Stage 4	3.242 (1.660–6.332)	**0.001**	3.917 (1.994–7.696)	**<0.001**
Tumor diameter	1.048 (1.003–1.095)	**0.034**	1.051 (1.006–1.098)	**0.025**
CA 125	1.001 (1–1.001)	**0.048**	1.001 (1–1.002)	**0.001**
Lymphadenectomy	0.249 (0.073–0.852)	**0.027**	0.425 (0.129–1.402)	0.160
Lymph node metastasis	2.372 (1.325–4.244)	**0.004**	2.598 (1.45–4.655)	**0.001**
Residual disease	2.029 (1.088–3.784)	**0.026**	2.076 (1.111–3.88)	**0.022**
Mesenchymal component (heterologous)	1.820 (0.996–3.328)	0.052	1.995 (1.093–3.644)	**0.025**
Epithelial component (non-endometrioid)	2.394 (1.32–4.344)	**0.004**	2.608 (1.432–4.749)	**0.002**
Multivariate				
Age	1.037 (0.993–1.082)	0.099	1.053 (1.011–1.097)	**0.014**
Lymphadenectomy	0.081 (0.021–0.314)	**<0.001**	0.094 (0.024–0.361)	**0.001**
Mesenchymal component (heterologous)	2.861 (1.196–6.841)	**0.018**	3.697 (1.572–8.695)	**0.003**

OR: odds ratio; CI: confidence interval; BMI (kg/m^{2}): body mass index; CA 125 (IU/mL): cancer antigen 125. Statistically significant values are indicated in bold

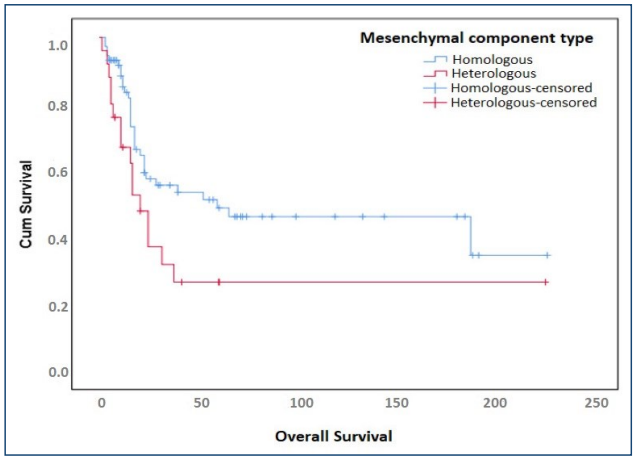

Figure 1. Overall survival graphics according to the type of mesenchymal component.

of early-stage patients in the study and the presence of heterologous components increasing disease progression and stage, resulting in detection at a lower rate in the early stages.

As supported by many studies in the literature, we also found that lymphadenectomy had a positive effect on OS in this study[1,10,13,15]. Although some studies claim that the number of lymph nodes resected is also effective, others claim that lymphadenectomy is strongly associated with OS[13,15]. However, in a similar study conducted by Ross et al., it was reported that pelvic lymph node dissection did not contribute to PFS but only increased OS, while paraaortic lymph node dissection had no effect on OS and PFS[16]. In contrast, the authors reported that the presence of LNM affected survival. In this study, the presence of LNM had a negative effect on both OS and DFS.

In UCs, adjuvant treatment is generally performed with radiotherapy, chemotherapy, or a combination of both[17,18]. In this study, multivariate analysis revealed that radiotherapy significantly improved OS and DFS. However, contrary to the literature, it was found that chemotherapy had no effect on survival[17,18]. This could be attributed to the fact that carcinosarcomas are already aggressive cancers and the vast majority of patients have received chemotherapy. However, 62.2% of our patients had received radiotherapy as adjuvant treatment.

The median age of UC onset is 62–67 years[19]. The median age of onset in the present study was consistent with the literature. In the multivariate analysis, age had no effect on OS and decreased DFS. Chen et al. evaluated 81 patients and reported that advanced age was a significantly worse prognostic factor in terms of both OS and PFS[20]. There are also studies in the

literature stating that age has no prognostic value in carcinosarcomas[11-13]. Worse DFS in advanced age could be attributed to the better response to adjuvant treatment in younger patients.

In uterine carcinomas, as in high-grade endometrial cancers, cancer stage, CA 125 elevation, LVSI positivity, presence of cervical invasion, presence of large tumor, presence of omental metastasis, and presence of residual tumor after surgery are associated with poor prognosis[1,3,5,6,16,19,21]. Consistent with the literature, it was also found in this study that these prognostic factors affected survival.

This study has several limitations. The study was designed retrospectively and conducted in a single center. In addition, although we were able to analyze the tumoral components of the patients effectively, we were unable to obtain clearer results because we could not detect how much of the tumor was covered by sarcoma or epithelial types in all patients. There is a need for further studies with a larger patient group and more detailed histopathological analysis that can specify the percentage of the tumor's heterologous component.

In conclusion, the results obtained in this study show that the coexistence of extrauterine sarcoma types with uterine tumors reduces life expectancy. It is difficult to conduct prospective studies because of the aggressive progression and short survival of carcinosarcomas. However, the results of this study are valuable because of the sufficient number of patients in a single tertiary center and the expert pathologists involved in the study. According to the findings of our study, a more decisive application of radiotherapy and chemotherapy combinations may improve survival and life expectancy in cases with a heterologous component.

ETHICAL APPROVAL

Ethical approval was obtained from the ethics committee of Tepecik Training and Research Hospital with decision number 2021/02-25.

AUTHORS' CONTRIBUTIONS

BC: Investigation, Project administration, Writing – original draft. **VK:** Conceptualization, Resources, Writing – original draft, Writing – review & editing. **İÇ:** Formal Analysis, Funding acquisition, Writing – original draft. **SS:** Data curation, Methodology, Writing – original draft. **KH:** Software, Validation, Writing – original draft. **OK:** Supervision, Visualization, Writing – original draft.

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