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Uterine Sarcoma and Carcinosarcoma: A Two-Center Experience in Iran

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Abstract

Background: Uterine sarcomas (US) represent a rare and heterogeneous spectrum of tumors characterized by diverse clinical behaviors and tumor responses. This study aims to assess patient and tumor characteristics and oncologic outcomes.

Method: This historical cohort study encompassed all patients with histologically confirmed diagnoses of the US who were referred to two oncology centers affiliated with Mashhad University of Medical Sciences (Iran) between March 2011 and April 2020. Data analyses were conducted using STATA version 14.02. Survival estimation was carried out utilizing the Kaplan-Meier method. The significance level was established at 0.05.

Results: A total of 33 patients were included in this study, comprising 23 with US and 10 with carcinosarcoma (CS). The mean age was 49.3 years for CS and 62.4 years for US (P = 0.0001). Nearly all patients were overweight, with a mean body mass index of 27.1 (confidence interval: 25.6-28.7). The majority of patients were diagnosed at an early stage. The Federation of Gynecology and Obstetrics (FIGO) stage, patient's anemia, and surgical resection were identified as significant prognostic factors. The median overall survival was 50.88 ± 5.7 months. The survival rates at 2, 3, and 5 years were 75%, 56%, and 41%, respectively. No significant difference was observed between CS and US regarding overall and disease-free survival.

Conclusion: Despite the typical early-stage diagnosis for US patients, the 5-year survival rate remains low. This study underscores the pivotal role of FIGO stage, tumor size, and surgical resection as vital prognostic factors for survival.

Keywords: Uterine neoplasms, Carcinosarcoma, Survival analysis, Prognosis

Introduction

Uterine Sarcomas (US) are a rare, heterogeneous group of tumors originating from mesenchymal cells. US makes up only 1% of all gynecological cancers,[1] and has a reported 5-year overall survival (OS) rate of 30-50%,[2,3] a comparatively worse outcome than other, more common, gynecological tumors. According to the World Health Organization 2020 classification, the subtypes of the US include:

- Leiomyosarcoma (LMS),
- Endometrial stromal sarcoma (ESS),
- Undifferentiated uterine sarcoma (UUS), and
- Adenosarcoma (AS)[4]

Historically, carcinosarcoma (CS) (previously called mixed malignant Mullerian tumor- MMMT) was classified as a US, but as data emerged in favor of it being a carcinoma with sarcomatoid differentiation,[5,6] it is now considered a highly malignant form of endometrial carcinoma.[4]

The etiology of the US is not very clear, but its association with obesity, diabetes, tamoxifen use, and radiation therapy has been shown in retrospective studies.[7-9] Some studies also implicate prior sex hormone use (oral contraceptives or hormone replacement therapy) in the etiology,[7,10,] but others put more importance on nulliparity and age at first birth, menopause, and menarche.[9,11]

Clinical features of the US are similar to uterine leiomyoma and could be misdiagnosed as such since they lack any specific findings on imaging. The FDA estimates that 1 in 225-550 women undergoing surgery for uterine fibroids are affected by US.[12] A missed diagnosis may lead to conservative surgeries and deteriorating oncologic outcomes;[13] hence, careful preoperative evaluations are needed. Colour Doppler ultrasonography and pelvic MRI are the preferred modalities in differentiating the two, with several indices proposed to improve specificity.[14]

Surgery has remained a cornerstone in the treatment of US: hysterectomy and complete surgical resection are proven to increase survival rates.[15,16] The role of adjuvant treatment is controversial since some have reported improved survival with adjuvant radiation therapy[2,3], and chemotherapy,[15] while others found no benefit.[16]

The US is a rare group of cancers with many uncertain features. Given the lack of research and available data on this disease, more studies are needed to help physicians make better treatment choices. We aimed to analyze patients who presented to two oncologic centers in Mashhad, the referral center for the Eastern part of Iran, from March 2011 to April 2020. This study evaluated and compared patient and treatment characteristics to their oncologic outcomes. Additionally, as CS has recently been separated from the US, those with this diagnosis were also collected, and their patient and treatment characteristics and outcomes were compared to those of the US.

Methods

Study design and data source

This historical cohort study received approval from the Mashhad University Medical Sciences' Review Board. It encompassed all patients referred to two oncology centers diagnosed with US or CS between March 2011 and April 2020. No exclusion criteria were applied during the review process. Patient data were obtained from medical records at the respective oncology centers. Consent was acquired during telephone interviews for academic purposes, and the study involved the analysis of de-identified patient data from existing medical records.

Data collection and variables

Data extraction from medical records encompassed the following variables: patient

characteristics (age, weight, body mass index (BMI), and menopausal status), presenting symptoms, histopathological diagnosis, stage at presentation, surgical treatment, and oncologic interventions. Oncologic interventions included chemotherapy, radiotherapy, or hormonal therapy. Furthermore, oncologic outcomes such as disease-free survival (DFS) and OS were documented. Patients were observed until their demise or until April 2022. Follow-up data included recurrence and cause of death. Patients were categorized as disease-free, alive with disease, deceased due to the disease, or deceased due to other causes. DFS was defined as the time from the termination of adjuvant treatment until the first treatment failure, while OS was defined as the time from the diagnosis of the disease until the time of death from any cause.

Statistical analysis

This study's descriptive and analytical analysis aimed to delineate patient characteristics and define OS and DFS in the US and CS population. The frequency of histological subtypes and treatment patterns were assessed for the descriptive analysis. Descriptive statistics were utilized to summarize the data. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means with standard deviations. Comparative analyses were conducted between the US and CS of the uterus. Chi-square tests or Fisher's exact tests were employed to compare categorical variables, and Student's t-test was used for continuous variables, as deemed appropriate. Cox regression analysis was employed for DFS and OS.

Ethical considerations

Approval from the Mashhad University Medical Sciences' Review Board was obtained with the ethical code of IR.MUMS.MEDICAL.REC.1399.386 prior to the initiation of data collection. Patient confidentiality was rigorously maintained throughout the study, and all data were meticulously de-identified to ensure privacy and anonymity.

Results

Patient and disease characteristics

In the study, a total of 33 patients were enrolled, with 23 diagnosed with US and 10 diagnosed with CS. Among the US group, the subtypes comprised 15 patients with LMS (65%), 6 with ESS (15%), one with AS, and one with UUS. The study population exhibited a mean age of 53.2 ± 9.66 years. However, patients with CS were notably older at diagnosis than those with US (62.4 years vs. 49.3 years, $P < 0.0001$). Postmenopausal status was more prevalent in the CS group (90% vs. 69.6%), although this distinction was not statistically significant. Most patients in both groups were overweight, with an average BMI of 27.1 ± 4.36 kg/m^2. Abnormal uterine bleeding (AUB) was the most prevalent presenting symptom in both subtypes, occurring in 54.5% of patients overall. Anemia upon presentation, defined as a hemoglobin level below 12 g/dl, was more frequent in the CS group, yet the difference did not reach statistical significance ($P = 0.287$). In both categories, patients were predominantly diagnosed at stage I. Tumor size was quantifiably larger in the US histopathology group (9.7 cm vs. 6.6 cm, $P = 0.2206$). Smoking history was recorded in two patients, with no history of alcohol consumption among the patients. Table 1 outlines the baseline characteristics of the patients and their comparison between the US and CS groups.

Treatment patterns

Surgery constituted the primary treatment modality in 90% of the study population (30 patients). Three patients did not undergo surgery due to unresectable local/metastatic disease or patient inoperability. Table 2

provides an overview of the treatment patterns in the two groups. None of the CS patients were observed post-surgery. In the US group, six patients were placed under observation due to early-stage disease, patient preference, or medical condition.

Follow-up and oncologic outcomes

The mean follow-up duration was 36.66 months (1-88 months). Among the total patients, 16 succumbed to cancer, with 11 deaths occurring in the US group and 5 in the CS group. Recurrence was observed in 14 patients, with 9 cases in the US group and 5 cases in the CS group. Two patients remained alive with the disease at the end of the study.

Survival analysis

The Kaplan-Meier method was employed to estimate the median OS and DFS, while the Cox regression model was utilized to estimate the hazard ratio and 95% confidence interval for OS and DFS. The median OS was 50.88 ± 5.7 months. The OS rates at 1, 2, 3, 4, and 5 years were 85%, 75%, 56%, 51%, and 41%, respectively. Single-variant analysis revealed associations between OS and stage and surgery. Unresectable cases exhibited a 19-fold higher risk of death due to disease, which was statistically significant. Neither adjuvant therapies (chemotherapy nor radiotherapy) displayed statistical significance. Each increase in stage elevated the likelihood of death by 3.99 times, which was significant. Each 1 cm increase in size resulted in a 5% increase in the risk of recurrence; however, this did not attain statistical significance. The presence of anemia increased the chances of recurrence fourfold, which was statistically significant. Table 3 illustrates the association of prognostic factors with survival.

Discussion

Analysis of a cohort of patients with US revealed that 65% of cases were characterized by LMS histology, making it the most common subtype. Patients with CS were predominantly postmenopausal and older, with the majority being in their sixth and seventh decades. The majority of patients were diagnosed in the early stages of the disease. Among the various prognostic factors affecting outcomes, the Federation of Gynecology and Obstetrics (FIGO) stage, patients' anemia, and surgical resection emerged as the most significant predictors of survival. Neither adjuvant chemotherapy nor radiotherapy significantly impacted the patients' survival rates.

Soft tissue sarcomas originating from the uterus encompass a heterogeneous group of tumors with varying clinical behaviors and responses to treatment.[17] Among these tumors, LMS is the most common histology, followed by ESS, UUS, and other rare subtypes, including AS. Age at presentation is another essential characteristic that distinguishes US with CS typically occurring in older individuals compared to ESS, which is more common in individuals aged 40 to 55 years.[18] Historically, CS was included in the US family; however, due to its different spread pattern and aggressive biology, it is now considered a metaplastic or dedifferentiated carcinoma. Higher mitotic index, frequent vascular invasion, and high metastatic potential have resulted in lower survival rates and specific treatment recommendations for CS.[19-21] The reported 5-year survival rate for CS is around 30%, and even 50% for those confined to the uterus.[22,23] However, the cohort found no significant differences in OS or DFS between US and CS. The limited number of patients in each group may have hindered the ability to detect statistical differences.

Almost all patients in the study are overweight. Although the exact etiology of the US is unknown, obesity is stated as a potential risk factor. Increased BMI is also a well-known risk factor in endometrial carcinoma, which supports the possible

biological similarity between uterine mesenchymal and epithelial tumors.[11]

In this analysis, advanced tumor stage and patient's anemia were found to have a negative impact on patient outcomes. The tumor stage is considered the most important prognostic factor in the US. The reported 5-year survival for the US is 50%-55% and 8%-12% in the early and advanced stage patients, respectively.[24] The 5-year OS in the patient cohort was 41%. According to FIGO classification, tumor size, and locoregional and distant dissemination determine stages I to IV. Each increase in stage from I to IV increased the chance of the patient's death by approximately fourfold, demonstrating the significant role of this variable. However, the FIGO staging system was revised in 2009 for uterine CS, as it does not accurately predict its distinct clinical behavior.[23]

Gynecologic malignancies, including the US, are among tumors with a higher prevalence of anemia at diagnosis. Abnormal uterine bleeding, nutritional deficits, and oncologic treatments are common reasons for anemia. Several studies have demonstrated the negative impact of anemia on patients' outcomes in cervical, ovarian, and endometrial cancer.[25,26] In the US, anemia is usually associated with other poor prognostic factors, including larger tumor size, advanced stage, and nodal involvement. There are multiple hypotheses to explain how a low hemoglobin level affects tumor control. Anemia, as a paraneoplastic syndrome due to cytokine secretion from tumor cells, tumor hypoxia resulting in tumor aggressiveness, as well as chemoradiotherapy resistance in hypoxic tumors are more commonly stated.[27]

The patients diagnosed with US had larger tumors compared to those with CS, and specifically, the analysis demonstrated worse survival rates with each 1-centimeter increment in tumor diameter. Tumor size is a well-known prognostic factor in the US. In the previous FIGO staging classification, stage I US was subdivided into IA and IB, according to whether the tumor size was less than or more than 5 centimeters.[28] Song et al. reported higher rates of early death and cancer-specific mortality among patients with tumors larger than 98 millimeters.[24]

In the cohort, patients who did not undergo surgery had the worst clinical outcomes. Surgical resection with negative margins is considered the mainstay of US treatment. The recommended procedure includes total abdominal hysterectomy and resection of any extra-uterine disease, with or without bilateral salpingo-oophorectomy or lymphadenectomy.[29] Although adjuvant radiotherapy and chemotherapy have been used in US treatment, the present study found no significant effect on survival outcomes.

Regarding adjuvant treatment, no compelling evidence supports the benefit of systemic or radiation therapy.[30,31] While some reports have found a beneficial effect of pelvic radiotherapy on local recurrence, it has not been shown to impact OS.[32,33] A nomogram developed by Junhong Du et al. identified patients with non-metastatic US who may benefit from radiotherapy based on prognostic stratification.[34] However, radiotherapy should only be recommended in patients with multiple adverse features, including higher grades, positive nodes, or involved surgical margins. Similarly, the data on adjuvant chemotherapy are inconclusive, with recent meta-analyses showing no significant decrease in recurrence rates in the treatment of early-stage LMS.[35] However, chemotherapy may be beneficial in histologic types with a higher risk of recurrence, including CS, high-grade ESS, uterine AS, and UUS.[36] According to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology-European Reference Network for rare adult solid cancers (ESMO-EURACAN) guidelines, chemotherapy should be reserved for higher-risk tumors (tumor spillage, tumor

morcellation, or higher grade) due to its toxicity.[37,38]

This study has several limitations that should be considered when interpreting the results. The study's retrospective design introduces inherent biases and limitations associated with data collection and analysis. The generalizability of the findings may be limited to the specific patient population and the selected oncology centers. Furthermore, the study's reliance on medical records introduces the possibility of missing or incomplete data, which could affect the accuracy and comprehensiveness of the analysis. Additionally, the study design precludes the establishment of causality and only allows for identifying associations and trends.

As this was a retrospective study, several patients were already deceased at the time of the study, which made collecting this information for a significant portion of the sample impossible. Therefore, this information was not included in the research and may have affected the results. Despite these limitations, this study provides important insights into the clinical characteristics, treatment patterns, and outcomes of patients with US and CS. Further research is needed to confirm these findings and to explore additional prognostic factors that may influence patient outcomes.

Conclusion

Although patients with the US are typically diagnosed in the early stages, the 5-year survival rate remains low. This study has demonstrated that the FIGO stage, the patient's anemia, and surgical resection are crucial prognostic factors for survival in patients with the US. No significant outcome difference was observed between patients with uterine CS and other histologic types of US.

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Conflict of Interest

None declared.

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Table 1. Patients' and tumors characteristics

Characteristic		Entire series (95% CI)	Uterine sarcoma (95% CI)	Carcinosarcoma of uterus (95% CI)	*P* – value
Number of patients		33	23	10	
Age		53.2 ± 9.67	49.26± 8.24	62.40 ± 5.70	
Body mass index		27.1 ± 4.36	26.63 ± 4.73	28.43 ± 3.22	0.62
Postmenopausal state		25 (75.8%)	16 (69.6%)	9 (90%)	0.17
Clinical presentation					
AUB		18 (54.5%)	12 (52.2%)	6 (60%)	
Abdominal pain		13 (39.4%)	8 (35.8%)	5 (50%)	
Abdominal mass		5 (15%)	4 (17.4%)	1 (10%)	
Stage at presentation					0.99
I		17 (51.5%)	12 (52.2%)	5(50%)	
II		7 (21.2%)	6 (26.1)	1(10%)	
III		7 (21.2%)	3 (13%)	4(40%)	
IV		2 (6.1%)	2 (8.7%)	0	
Anemia on presentation		19(57.6%)	12 (52.20%)	7(70.00%)	0.79
Tumor Grade	1	5 (22.73%)	4 (23.53%)	1 (20.00%)	0.63
	2	2 (9.09%)	1 (5.88%)	1 (20.00%)	
	3	15	12 (70.59%)	3 (60.00%)	
Tumor size		8.75 (±6.24)	9.76 (±6.89)	6.62 (±4.13)	0.01
Tumor location	Fundus	5 (15.15%)	2 (8.70%)	3 (30.00%)	0.28
	Body	25 (75.76%)	19 (82.61%)	6 (60.00%)	
	Inferior segment	3 (9.09%)	2 (8.70%)	1 (10.00%)	

CI: Confidence interval; AUB: Abnormal uterine bleeding

Table 2. Treatment patterns of patients and their comparison between US and CS of uterus

Pathology / Treatment		CS	US		
			LMS	EES	Others
Surgery alone		0	5 (33.3%)	3 (50%)	0
Surgery+ adjuvant treatment		9 (90%)	10 (66.7%)	2 (33%)	1 (50%)
	RT	1	5	2	-
	RT+chemotherapy	5	1	-	1
	Chemotherapy	3	2	-	-
Chemotherapy± RT		1(10%)	0	1 (17%)	1 (50%)

CS: Carcinosarcoma; US: Uterine sarcoma; LMS: Liomyosarcoma; EES: Endometrial stromal sarcoma; RT: Radiotherapy

Table 3. Single variant analysis and DFS and OS

	DFS			OS		
Variable	**HR**	**CI**	***P* value**	**HR**	**CI**	***P* value**
Age	1.04	0.97-1.12	0.19	0.99	0.30-1.06	0.98
Anemia	0.75	0.57- 0.99	0.01	0.84	0.66-1.03	0.26
Menopausal status	2.42	0.53-10.1	0.24	1.53	0.42-5.49	0.51
Pathology (CS VS. US)	0.36	0.4-2.7	0.36	0.99	0.32-3.12	0.65
Size	1.05	0.98-1.12	0.20	1.02	0.95-1.10	0.54
Stage (Early vs. Advanced)	3.17	1.17-8.54	0.02	3.99	1.36-11.74	0.01
Surgery	-*	-*	-*	0.03	0.005-0.21	0.00
Radiotherapy	0.64	0.22-1.83	0.41	0.56	0.21-1.53	0.26
Chemotherapy	1.17	0.32-4.21	0.81	0.64	0.23-1.76	0.38

* Patients who did not undergo surgery did not attain disease-free statusl DFS: Disease-free survival; OS: Overall survival; CI: Confidence interval; HR: Hazard ratio; CS: Carcinosarcoma; US: Uterine sarcoma