Gynecology; *and Gynecological Oncology*

The Evaluation of Uterine Sarcomas: Tertiary Center Experience

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ABSTRACT

OBJECTIVES: To elucidate prognostic factors, determine the best course of treatment methods, and assess oncological results in individuals diagnosed with uterine sarcoma.

STUDY DESIGN: Between January 2001 and August 2023, 30 patients with uterine sarcomas (US) were included and analyzed in this cross-sectional study. Sixteen patients (53.3%) had uterine leiomyosarcoma, 6 patients (20%) had high-grade endometrial stromal sarcoma, 8 patients (26.7%) had low-grade endometrial stromal sarcoma.

RESULTS: The median follow-up of all participants was 50 months. Recurrence was detected in 43.3% of the patients. 5-year survival ratio was 73.3%, 5-year disease-free survival ratio was 66.7%, the overall survival ratio was 70% and the overall disease-free survival rate was 56.6%. No difference was observed between groups in terms of survival comparisons. No statistically significant effect of adjuvant systemic chemotherapy, adjuvant radiotherapy, and combined treatments on median overall survival and median disease-free survival was detected (p>0.05).

CONCLUSION: Uterine sarcomas are uncommon malignancies characterized by a poor prognosis, even in early stages, and they are associated with a high recurrence ratio. The most effective treatment method remains unclear to date.

Keywords: Endometrial stromal sarcoma; Leiomyosarcoma; Treatment; Uterine sarcoma

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Introduction

Uterine sarcomas (US) are an uncommonly violent malignancy of the uterine corpus. Their annual incidence is 0.3/100,000 and uterine corpus-derived malignancies constitute 3-9% of all such malignancies (1,2). Based on their histological characteristics, they can alternatively be categorized as mixed epithelial and mesenchymal tumors or mesenchymal tumors. Uterine leiomyosarcoma (u-LMS), which accounts for 63% of mesenchymal tumors; high-grade endometrial stromal sarcoma (HGESS), low-grade endometrial stromal sarcoma (LGESS), and undifferentiated uterine sarcoma (UUS), which account for 21%; adenosarcoma (AS), which accounts for 6%; and a few other infrequent types make up the remaining 10% (3). The distinctive characteristics of uterine leiomyosarcoma (u-LMS) manifest predominantly as a sizable tumor, typically observed in women over the age of 40. Notably, u-LMS tends to exhibit a high-grade pathology, characterized by a mitotic rate of more than 15 per 10 high-power fields (HPF). Prognostically, the outlook is unfavorable, marked by a significant recurrence rate ranging from 53% to 71% (4). Kapp et al. reported that five-year disease-free survival (DFS) of u-LMS was 60-70% for the early stage and 29% for the advanced stage (5). LGESS is characterized by its estrogen and progesterone receptor positivity, typically manifesting in women over the age of 40. Importantly, the overall prognosis for LGESS is generally favorable, with a five-year survival rate of 89% for early-stage cases, in contrast to 50% for advanced-stage instances. Recurrence is observed in approximately one-third of cases (6). HGESS typically exhibits negativity for estrogen and progesterone receptors, and it is characterized by a heightened recurrence rate, often occurring earlier following the primary diagnosis. The overall survival (OS) rate for all stages of both LGESS and HGESS is reported as 72.7% (7).

The optimal management and identification of prognostic factors for the US remain challenging due to their diverse histological subtypes and rarity (8). Many studies have suggested

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that tumor size and mitotic figures are important prognostic indicators (9,10). Total abdominal hysterectomy (TAH) combined with bilateral salpingo-oophorectomy (BSO) is the usual first therapy in the US. Many studies estimate a pelvic lymph node involvement rate as high as 47%, while the significance of pelvic lymph node dissection (PLND) is still being investigated (11). However, no significant survival benefit has been consistently demonstrated after PLND dissection (12). Adjuvant treatment options for the US are limited, and their efficacy is a subject of ongoing investigation. According to a comprehensive study, adjuvant chemotherapy does not appear to improve survival in u-LMS patients (13). Similarly, no survival advantage has been reported associated with adjuvant radiotherapy in US cases (7). The intricacies of managing the US underscore the need for further research to establish effective therapeutic strategies and refine prognostic indicators.

The objective of our study was to elucidate risk factors, determine the best course of treatment, and assess oncological results in individuals diagnosed with US.

Material and method

This retrospective cross-sectional clinical study was carried out at a tertiary facility. Informed consent was received from all participants involved in the research, and the research was conducted in accordance with the principles outlined in the Helsinki Declaration. Institutional ethics committee approval was provided (Date: 14/12/2022, approval number: 2022/40-16). Between January 2001 and August 2023, 30 US patients were included and analyzed in this study. 16 patients (53.3%) had u-LMS, 6 patients (20%) had HGESS, and 8 patients (26.7%) had LGESS. A qualified pathologist thoroughly examined all of the histology samples from the records, and the initial diagnoses were validated. Patients aged 18 years and older with biopsy-proven US according to the WHO classification were included in the study (14,15). Individuals with incomplete data who were diagnosed with malignant mixed Müllerian tumors, commonly known as uterine carcinosarcoma, were not allowed to participate in the study. Uterine carcinoma is the current classification for these malignancies. Patients with metastatic sarcoma from other gynecological sites, those with distant disease at presentation (FIGO stage IVB), and those lacking complete data on pathological diagnosis, clinical findings, and subsequent studies for analysis were likewise excluded. Participants who neglected follow-up visits after the first diagnosis were covered by this exclusion criterion. Clinical data and the whole of the medical history were assessed for every record.

Adjuvant chemotherapy is used in cases of recurrent or advanced non-LGESS and hormone-unresponsive ESS. Chemotherapy regimens include compounds such as anthracyclines, dacarbazine, vinorelbine, gemcitabine, docetaxel, and temozolomide. These cytotoxic drugs were administered as monodrugs or multidrugs. Adjuvant radiotherapy was planned in the presence of local signs of disease in the presence of recurrent ESS.

Computed tomography (CT) scans of the abdomen and pelvis, with or without a CT scan of the chest, and magnetic resonance imaging (MRI) of the pelvis were performed on all patients as part of baseline imaging tests. Depending on the primary surgeon's judgment, these imaging scans were carried out four weeks before surgery or between 4 and 6 weeks following surgery. Furthermore, scans were carried out from 8 to 12 weeks following the final dose of adjuvant systemic treatment. Some patients also had disease assessment scans performed after completing three or four rounds of systemic chemotherapy.

Retrospective record reviews were used to document the systematical follow-up scans. In the early years, these follow-up scans were planned every 3 to 6 months; in the following years, the scans were scheduled every 6 to 12 months. The duration in months between the diagnosis and the date of the last follow-up or the return of the disease was the definition of DFS. The length of time, expressed in months, between the diagnosis date and the date of death or the final follow-up was the definition of OS.

Statistical analysis was conducted using SPSS version 26.0 (IBM Inc., Chicago, IL, USA). The normality of the distribution was assessed using the Kolmogorov-Smirnov test. Parameters that were not normally distributed were analyzed using the Kruskal-Wallis test followed by post hoc tests. The analysis of categorical data utilized the Chi-square test and Fisher’s exact test. Quantitative data were expressed as median (minimum-maximum), while qualitative data were presented as numbers and percentages (%). Survival analysis was performed using the Kaplan-Meier test and log-rank comparison. A p-value less than 0.05 was considered statistically significant.

Results

In our study, 30 patients with US were analyzed. Sixteen patients (53.3%) had u-LMS, 6 patients (20%) had HGESS, and 8 patients (26.7%) had LGESS. Demographic characteristics of patients classified by histological type were summarized in Table I. The median age of all patients was 47 (26-75), with u-LMS patients found to have a median age group of 47.5 (35-75), HGESS with 53.5 52 (32-74), LGESS with 41.5 (26-64) (p=0.2). Classified age and menopausal status were similar between the groups (p=0.2; p=0.5, respectively). There was no difference between the groups with regard to gravide, parity, and abortion (p=0.7; p=0.4; p=0.8 respectively). Nulliparity was detected as 12.5% in the u-LMS group. No nulliparous patients were detected in either the HSESS or LGESS groups (p=0.3). The most frequent clinical symptom was vaginal bleeding in each group. However, clinical symptoms were similar between groups (p=0.5).

Table I: *Demographic characteristics of patients classified by histological type*

dapagliflozin	Group 1 (u-LMS) (n=16, 53.3%)	Group 2 (HGESS) (n=6, 20%)	Group 2 (LGESS) (n=8, 26.7%)	All patients (n=30, 100%)	p
Age (years)	47.5 (35-75)	52 (32-74)	41.5 (26-64)	47 (26-75)	0.2
Classified of age (n, %)					0.2
<50 years	56.2% (9/16)	33.3% (2/6)	75% (6/8)	56.6% (17/30)	
≥50 years	43.8% (7/16)	66.7% (4/6)	25% (2/8)	43.4% (13/30)	
Menstrual status (n, %)					0.5
Premenopausal	50% (8/16)	33.3% (2/6)	62.5% (5/8)	50% (15/30)	
Postmenopausal	50% (8/16)	66.7% (4/6)	37.5% (3/8)	50% (15/30)	
Gravida	2.5 (0-6)	3 (1-7)	2.5 (1-9)	3 (0-9)	0.7
Parity	1 (0-4)	2.5 (1-4)	2 (1-4)	1.5 (0-4)	0.4
Abortion	1 (0-2)	0.5 (0-4)	1 (0-7)	1 (0-7)	0.8
Nulliparity (n,%)	12.5% (2/16)	0% (0/6)	0% (0/8)	6.6% (2/30)	0.3
Clinical symptoms (n, %)					
Pelvic/abdominal mass	12.5% (2/16)	16.6% (1/6)	12.5% (1/8)	13.3% (4/30)	0.5
Pelvic pain	31.2% (5/16)	0% (0/6)	12.5% (1/8)	20% (6/30)	
Vaginal bleeding	56.3% (9/16)	83.4% (5/6)	75% (6/8)	66.7% (20/30)	

Tumor characteristics of patients classified by histological type are listed in Table II. The highest rate of malignancy according to preoperative endometrial biopsy reports was in the HGESS group, at 33.3%. When all patients were evaluated, preoperative biopsy could not pathologically distinguish malignant from benign in 40%. There was no difference between the groups in terms of preoperative biopsy results (p=0.5). LDH and CA-125 values were similar between the groups (p=0.2; p=0.1, respectively). Of all patients, 63.3% were in FIGO stage I. While FIGO stage I was 75% in the LGESS group, FIGO stage IV was present in 37.5% of the u-LMS group. Additionally, FIGO stage III was present in 25% of the LGESS group. There were significant differences between the groups in terms of FIGO stage (p=0.04). The group with the largest tumor size and the highest tumor size ratio of ≥5 cm was u-LMS (p=0.001). The groups were similar with regard to the number and location of masses (p=0.2; p=0.1, respectively). Histological grade was defined as sarcomas very similar to normal adult mesenchymal tissue (well-differentiated), sarcomas with definite histological type (moderately differentiated), and sarcomas of suspicious type (poorly differentiated). The well-differentiated histological grade was found to be highest in the LGESS group at 87.5%, while the poorly differentiated histological grade was highest in the HGESS group at 83.4%. The groups differed in terms of histological grade (p=0.001). While a mitotic count of 0-10 was highest in the LGESS group at 62.5%, a mitotic count >20 was highest in the HGESS group at 83.4% (p<0.001; p<0.001, respectively). Tumor necrosis ≥50% was highest in the HGESS group at 83.4% (p=0.03). Lymphovascular invasion, lymph node status, and pelvic wash were similar between the groups (p=0.8; p=0.2; p=0.6, respectively).

Evaluation of surgical and medical treatments by histological type are shown in Table III. Surgery type and frozen section were similar between groups (p=0.3; p=0.1, respectively). In the LGESS group, the ovaries of three patients were preserved. In addition, these patients were given medroxyprogesterone acetate treatment to prevent recurrence. These patients had a desire for fertility. These are cases in FIGO stage 1. The primary surgeons decided during the operation whether a frozen section would be performed or not. In the HGESS group, all participants were received adjuvant chemotherapy (p=0.001). Therefore, 11 patients did not have a frozen section evaluation. In the LGESS group, 75 of the participants did not receive chemotherapy. The monodrug regimen was highest in the HSESS group at 33.3% and the multidrug regimen u-LMS at 87.5% (p=0.01; p<0.01; p=0.001, respectively). Number of chemotherapy regimen cycles median value was highest in u-LMS and HGESS groups (p<0.01). There was no difference between the groups with regard to adjuvant radiotherapy received, number of radiotherapy regimen cycles, and treatment modality (p=0.8; p=0.3; p=0.08, respectively).

Treatment outcomes of patients classified by histological type are listed in Table IV. The median follow-up of all participants was 50 months (2-219). The median follow-up of the groups was similar (p=0.4). Recurrence was detected in 43.3% of the patients. The most common site of recurrence was the lung (46.1%). The median time to recurrence was 23 months (3-219). Follow-up, retention, recurrence location, and time of recurrence were not different between groups (p=0.4; p=0.4; p=0.5; p=0.1, respectively). OS was shown in Figure 1 and disease-free survival (DFS) was shown in Figure 2. The 5-year survival rate was found to be 73.3%, The 5-year DFS rate was 66.7%, the OS rate was 70% and overall DFS was 56.6%.

Table II: *Tumor characteristics of patients classified by histological type*

Variables	Group 1 (u-LMS) (n=16, 53.3%)	Group 2 (HGESS) (n=6, 20%)	Group 2 (LGESS) (n=8, 26.7%)	All patients (n=30, 100%)	p
Preoperative biopsy reports (n, %)					0.5
Malign	25% (4/16)	33.3% (2/6)	12.5% (1/8)	23.3% (7/30)	
Benign	25% (4/16)	50% (3/6)	50% (4/8)	36.7% (11/30)	
Undetermined	50% (8/16)	16.7% (1/6)	37.5%(3/8)	40% (12/30)	
LDH (U/L)	238 (134-481)	344 (134-496)	296 (246-356)	296 (134-496)	0.2
CA-125 (mg/dL)	18 (3-92)	11 (3.2-15)	11.3 (1.1-42)	14.8 (1.1-92)	0.1
FIGO stage (n, %)					0.04
I	62.5% (10/16)	50% (3/6)	75% (6/8)	63.3% (19/30)	0.6
II	0% (0/16)	16.6% (1/6)	0% (0/8)	3.4% (1/30)	0.1
III	0% (0/16)	0% (0/6)	25% (2/8)	6.7% (2/30)	0.03
IV	37.5% (6/16)	33.3% (2/6)	0% (0/8)	26.8% (8/30)	0.1
Tumor size (cm)	8.5 (5-26)	4.7 (4-7)	2.7 (1-10)	7 (1-26)	0.001
Classified of tumor size (n, %)					0.001
<5cm	0% (0/16)	50% (3/6)	62.5% (5/8)	26.6% (8/30)	
≥5 cm	100% (16/16)	50% (3/6)	37.5% (3/8)	73.4% (22/30)	
Number of mass (n)	1 (1-5)	1.5 (1-3)	1 (1-2)	1 (1-5)	0.2
Location of mass (n, %)					0.1
Submucosal	18.7% (3/16)	66.7% (4/6)	62.5% (5/8)	40% (12/30)	
Intramural	68.7% (11/16)	16.6% (1/6)	37.5% (3/8)	50% (15/30)	
Subserous	6.2% (1/16)	0% (0/8)	0% (0/8)	3.3% (1/30)	
Mixed	6.2% (1/16)	16.6% (1/6)	0% (0/8)	6.7% (2/30)	
Histological grade (n, %)					0.001
Well-differentiated	12.5% (2/16)	16.6% (1/6)	87.5% (7/8)	33.3% (10/30)	0.001
Moderately-differentiated	43.7% (7/16)	0% (0/6)	12.5% (1/8)	26.6% (8/30)	0.06
Poor-differentiated	43.7% (7/16)	83.4% (5/6)	0% (0/8)	40% (8/30)	<0.001
Mitotic count/10 HPF (n, %)					<0.001
0-10	6.2% (1/16)	16.6% (1/6)	62.5% (5/8)	23.3% (7/30)	<0.001
10-20	56.2% (9/16)	0% (0/6)	37.5% (3/8)	40% (12/30)	0.05
>20	37.6% (6/16)	83.4% (5/6)	0% (0/8)	36.7% (11/30)	<0.001
Tumor necrosis (n, %)					0.03
None	25% (4/16)	0% (0/6)	50% (4/8)	26.6% (8/30)	0.1
<50%	25% (4/16)	16.6% (1/6)	50% (4/8)	30% (9/30)	0.3
≥50%	50% (8/16)	83.4% (5/6)	0% (0/8)	43.4% (13/30)	<0.001
Lymphovascular invasion (n, %)					0.8
Positive	37.5% (6/16)	33.3% (2/6)	25% (2/8)	33.3% (10/30)	
Negative	62.5% (10/16)	66.7% (4/6)	75% (6/8)	66.7% (20/30)	
Lymph node status (n, %)					0.2
Negative	37.5% (6/16)	33.3% (2/6)	62.5% (5/8)	43.3% (13/30)	
Positive	0% (0/16)	16.6% (1/6)	0% (0/8)	3.3% (1/30)	
None (No lymph node dissection was performed)	62.5% (10/16)	50% (3/6)	37.5% (3/8)	53.3% (16/30)	
Pelvic wash (n, %)					
Positive	0% (0/16)	0% (0/6)	0% (0/8)	0% (0/30)	0.6
Negative	75% (12/16)	83.4% (5/6)	62.5%(5/8)	73.3% (22/30)	
None	25% (4/16)	16.6% (1/6)	37.5% (3/8)	26.7% (8/30)	

Table III: *Evaluation of surgical and medical treatments by histological type*

Variables	Group 1 (u-LMS) (n=16, 53.3%)	Group 2 (HGESS) (n=6, 20%)	Group 2 (LGESS) (n=8, 26.7%)	All patients (n=30, 100%)	p
Surgery type (n, %)					0.3
TAH + BS + ovarian conservation	18.8% (3/16)	0% (0/6)	37.5% (3/8)	20% (6/30)	
TAH+BSO	50% (8/16)	50% (3/6)	50% (4/8)	50% (15/30)	
TAH+BSO+PLND	31.2% (5/16)	50% (3/6)	12.5% (1/8)	30% (9/30)	
Frozen section (n, %)					0.1
Benign	0% (1/16)	0% (0/6)	12.5% (1/8)	3.3% (1/30)	
Malign	31.2% (5/16)	16.6% (1/6)	50% (4/8)	33.3% (10/30)	
Undetermined	0% (0/16)	16.6% (1/6)	0% (0/8)	3.3% (1/30)	
None	68.8% (11/16)	66.8% (4/6)	37.5% (3/8)	60% (18/30)	
Adjuvant chemotherapy received (n,%)	87.5% (14/16)	100% (6/6)	25% (2/8)	73.3% (22/30)	0.001
Chemotherapy regimen (n, %)					<0.001
No	12.5% (2/16)	0% (0/6)	75% (6/8)	26.6% (8/30)	0.01
Monodrug	0% (0/16)	33.3% (2/6)	0% (0/8)	6.7% (2/30)	<0.01
Multidrug	87.5% (14/16)	66.7% (4/6)	25% (2/8)	66.7% (20/30)	0.001
Number of chemotherapy regimen cycles (n)	6 (0-12)	6 (4-12)	0 (0-6)	6 (0-12)	<0.01
Adjuvant radiotherapy received (n,%)	75% (12/16)	66.7% (4/6)	75% (6/8)	73.3% (22/30)	0.8
Number of radiotherapy regimen cycles (n)	25 (0-27)	25 (0-25)	25 (0-25)	25 (0-27)	0.3
Treatment modality (n, %)					0.08
Surgery alone	6.2% (1/16)	0% (0/6)	25% (2/8)	10% (3/30)	
Surgery + radiotherapy	6.2% (1/16)	16.6% (1/6)	50% (4/8)	20% (6/30)	
Surgery+ chemotherapy	18.7% (3/16)	16.6% (1/6)	0% (0/8)	13.3% (4/30)	
Surgery+radiotherapy+chemotherapy	68.8% (11/16)	67.8% (4/6)	25% (2/8)	56.7% (17/30)	

Table IV: *Treatment outcomes of patients classified by histological type*

Variables	Group 1 (u-LMS) (n=16, 53.3%)	Group 2 (HGESS) (n=6, 20%)	Group 2 (LGESS) (n=8, 26.7%)	All patients (n=30, 100%)	p
bFollow-up (months)	50 (5-197)	28.5 (6-219)	90 (27-204)	50 (5-219)	0.4
Recurrence (n, %)	50% (8/16)	50% (3/6)	25% (2/8)	43.3% (13/30)	0.4
Recurrence location (n, %)					0.5
Pelvis	0% (0/8)	33.3% (1/3)	50% (1/8)	15.3% (2/13)	
The abdominal cavity outside the pelvis	37.5% (3/8)	33.3% (1/3)	0% (0/8)	30.7% (4/13)	
Lung	50% (4/8)	33.3% (1/3)	50% (1/8)	46.1% (6/13)	
Liver	12.5% (1/8)	33.3% (1/3)	0% (0/8)	7.6% (1/13)	
Time of recurrence (months)	12 (6-71)	23 (3-219)	166 (162-170)	23 (3-219)	0.1
5 years survival (n,%)	62.5% (10/16)	66.6% (4/6)	100% (8/8)	73.3% (22/30)	0.1
5 years of disease-free survival (n,%)	50% (8/16)	66.6% (4/6)	100% (8/8)	66.7% (22/30)	0.05
Overall survival (n,%)	56.2% (9/16)	66.6% (4/6)	100% (8/8)	70% (21/30)	0.08
Overall survival (months)	50 (5-197)	28.5 (6-219)	90 (27-204)	50 (5-219)	0.4
Overall disease-free survival (n,%)	8/16 (50%)	50% (3/6)	75% (6/8)	56.6% (17/30)	0.4
Overall disease-free survival (months)	45 (5-198)	25 (3-219)	90 (27-170)	47.5 (3-219)	0.2

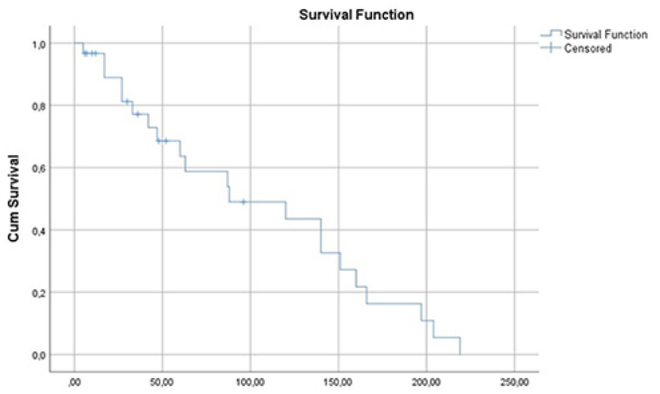

Figure 1: *Overall survival*

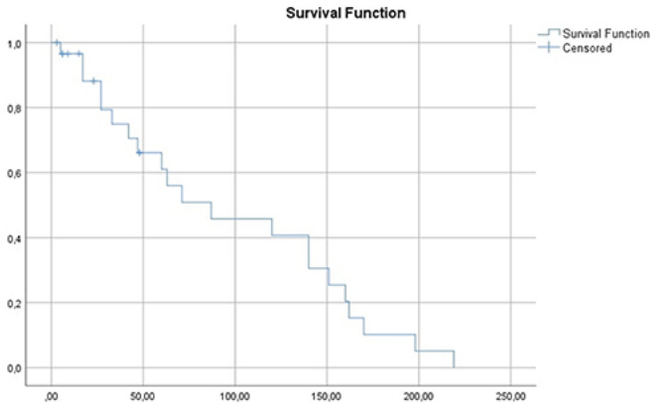

Figure 2: *Overall disease-free survival*

The median OS was 50 months (5-219) and the median overall DFS was 47.5 months (3-219). No difference was observed among groups with regard to survival comparisons.

Overall survival by histology is shown in Table IV and Figure 3. The median OS in all sarcoma subtypes was 50 (5-197) months in u-LMS, 28.5 (6-219) months in HGESS, and 90 (27-204) months in LGESS (p=0.08). OS by FIGO classification is shown in Figure 4. The median OS for each FIGO stage was determined to be 87 (5-204) months for stage 1, 6 (6-6) months for stage 2, 106.5 (47-166) months for stage 3, and 36 (5-219) months for stage 4 (p=0.3). Figure 5 shows the overall survival in all patients, with and without adjuvant systemic treatment. Participants who had adjuvant systemic chemotherapy (with or without radiotherapy) had a median overall survival of 50 (6-219) months; those who did not get adjuvant chemotherapy had a median OS of 53.5 (5-204) months (p=0.3). Figure 6 displayed the DFS for every participant, whether they received adjuvant systemic chemotherapy or not. Individuals who had adjuvant systemic chemotherapy (with or without radiotherapy) had a median disease-free survival (DFS) of 45 (3–219) months, whereas those who did not receive adjuvant chemotherapy had a median DFS of 53.5 (5-170) months (p=0.1). Figure 7 shows the overall survival in all patients, with and without adjuvant radiotherapy treatment. Participants who got adjuvant radiotherapy (with or without chemotherapy) had a median overall survival of 63 (6-219) months; those who did not get adjuvant radiotherapy had a median OS of 12 (5-204) months (p=0.4). Figure 8 displayed the DFS for every participant, whether they received adjuvant radiotherapy or not. Individuals who had adjuvant systemic radiotherapy (with or without chemotherapy) had a median DFS of 60 (3–219) months, whereas those who did not receive adjuvant radiotherapy had a median DFS of 9 (5-170) months (p=0.1). Figure 9 shows the overall survival in all patients, with combined treatment. Participants who received combined treatment had a median overall survival of 87 (27-219) months; those who did not get combined treatment had a median OS of 17 (5-204) months (p=0.09). Figure 10 displayed the DFS for every participant, whether they received combined treatment or not. Individuals who received combined treatment had a median DFS of 63 (6-219) months, whereas those who did not receive combined treatment had a median DFS of 17 (3-170) months (p=0.06).

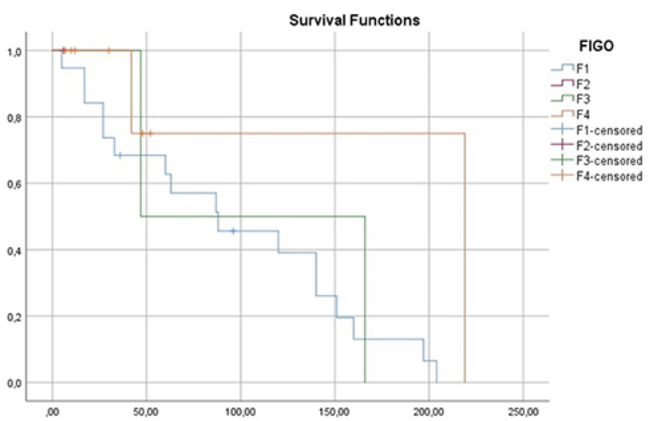

Figure 3: *Overall survival by histology.*

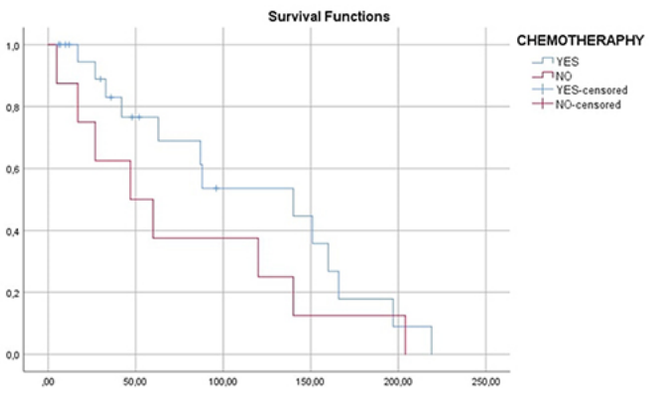

Figure 4: *Overall survival by FIGO classification.*

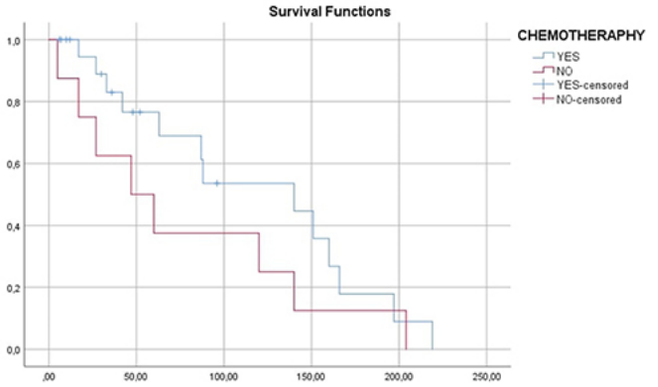

Figure 5: *Overall survival in all patients with/without adjuvant systemic chemotherapy.*

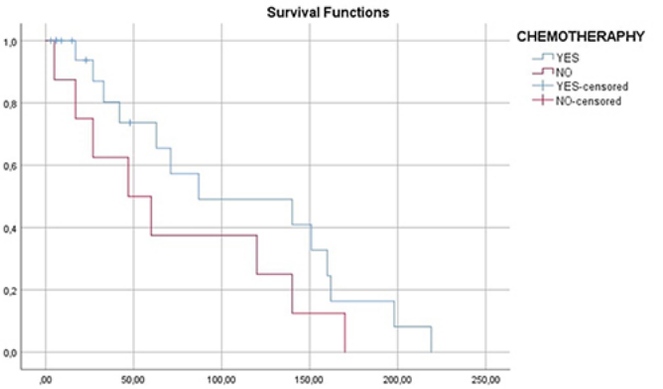

Figure 6: *Disease-free survival in all patients with/without adjuvant systemic chemotherapy*

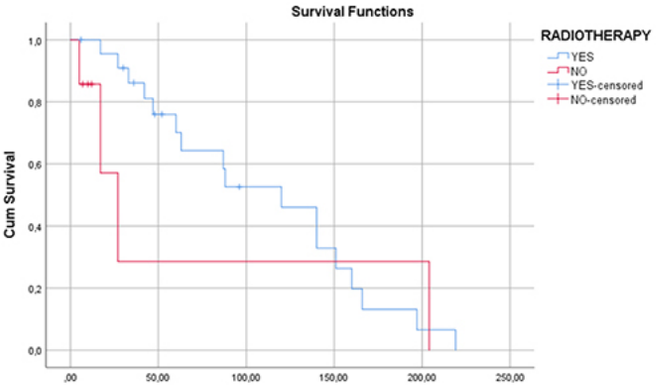

Figure 7: *Overall survival in all patients, with and without adjuvant radiotherapy.*

Figure 8: *Disease-free survival in all patients with/without adjuvant radiotherapy.*

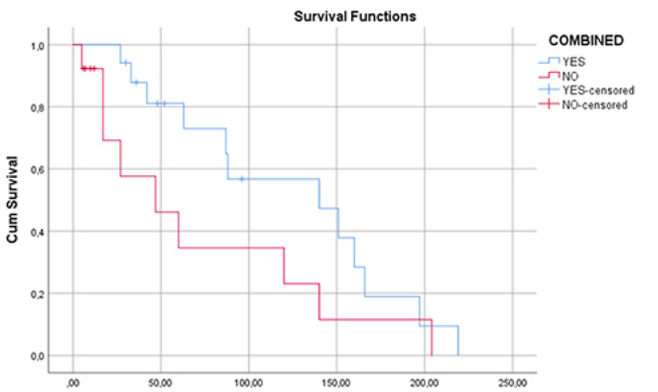

Figure 9: *Overall survival in all patients, with combined treatment.*

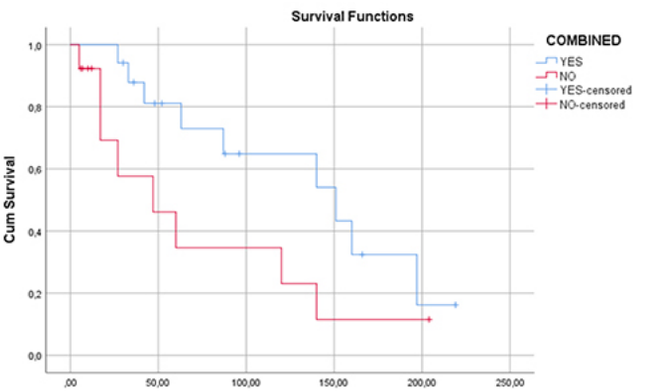

Figure 10: *Disease-free survival in all patients with combined treatment.*

Discussion

A heterogeneous group of malignancies, US, are extremely rare. Recent advancements in research have revealed that specific chromosomal translocations leading to gene fusion and subsequent transcription factor activation contribute to the increased incidence of US and their various subtypes (3).

The histopathological examination of our cohort, consisting of 30 individuals with the US, identified u-LMS as the predominant subtype, constituting 53.3% of the total research subjects. This finding aligns with the literature, further supporting the observation that u-LMS is the most prevalent subtype within the spectrum of US (3,16).

The median age in our research group was 47 years (26-75). This demographic profile was consistent with findings reported in previously published studies (3,16,17). The majority of participants typically had symptoms such as vaginal bleeding, the presence of a pelvic or abdominal mass, and pelvic pain (2,3). In this research, the most common clinical symptom was vaginal bleeding in each group.

The advantages of preoperative sampling are manifold. In addition to aiding in the conclusive diagnosis of US, preoperative sampling facilitates the formulation of precise surgical plans for surgeons. According to literature reports, preoperative biopsies have indicated invasive malignancy in 86-89% of US patients, underscoring the diagnostic significance of this procedure. In our study, this rate was found to be 23.3%. Since preoperative sampling was not performed by a single surgical team, our conclusion may be lower than the literature data.

For the US, total abdominal hysterectomy plus bilateral salpingo-(TAH+BSO) is the most effective initial therapy (11). In our study, 50% of the participants underwent this standard surgical procedure. One-third of the patients underwent PLND. In the literature, the rate of PLND varies between 30% and 74% (17). Nevertheless, no significant survival benefit of PLND has been observed (17). Concerns for ovarian conservation are a recurring issue among young girls having gynecological surgery. In cases where only women of reproductive age and the uterus are affected by the condition, there is an option to preserve both the uterus and ovaries (5,18). One-fifth of the patients in our study were suitable for ovarian preservation, and these patients were in the u-LMS and LGESS groups.

Data evaluating the effectiveness of radiation treatment or chemotherapy after surgery for individuals with US are limited. The Gynecological Oncology Group (GOG) conducted a clinical trial with 156 cases of early-stage US and found that postoperative doxorubicin decreased the recurrence rate in comparison with observation (41% vs. 53%) (19). Still, no appreciable effect on OS or DFS was noted (19). Another prospective trial with 25 women with stage I-IV u-LMS, found that the whole cohort's median DFS was 13 months when gemcitabine and docetaxel were used together (20). However, the study lacked a control arm, making it challenging to draw conclusive observations regarding its impact on OS. The combined usage of gemcitabine and docetaxel accompanied by doxorubicin failed to result in a decreased recurrence rate or an increase in survival in a prospective multicenter phase 2 study focused on early-stage US (21). In a real-world investigation of US patients with carcinosarcoma, similar findings of no evident survival advantage were reported (16,17,22). In their research, Khan et al. said that adjuvant systemic chemotherapy was administered to 60% of patients, mostly in the form of a gemcitabine and docetaxel combination (23). The median DFS for individuals who received systemic chemotherapy was determined to be 13.5 months, whereas patients without adjuvant chemotherapy had a median DFS of 11 months (23). This observed difference was found to be statistically significant. However, in the survival analysis, no discernible difference in OS was noted between the two groups (23). In our study, the median OS for individuals who received adjuvant systemic chemotherapy was 50 months (6-219), whereas it was 53.5 months (5-204) for individuals who did not have adjuvant chemotherapy. Interestingly, there was no statistically significant difference in OS between individuals who took adjuvant chemotherapy and those who did not. Similarly, the median DFS for individuals who had adjuvant systemic chemotherapy was 45 months (3-219 months), whereas it was 53.5 months (5-170 months) for individuals who did not take adjuvant chemotherapy. In concordance with OS, no statistically significant difference in DFS was observed between individuals who had adjuvant chemotherapy and those who did not.

It is reported in the literature that the group with the maximum survival based on histological subtypes and FIGO (International Federation of Gynecology and Obstetrics) staging is u-LMS and stage 1 patients (17,23). In our study, the median OS in each sarcoma subtype was 50 (5-197) months in u-LMS, 28.5 (6-219) months in HGESS, and 90 (27-204) months in LGESS. Between the groups, there existed no statistically significant difference. It is plausible that the variation in results between our study and the existing literature might be attributed to the limited number of individuals with high-grade endometrial stromal sarcoma (HGESS) and the absence of FIGO stage IV patients in the low-grade endometrial stromal sarcoma (LGESS) group. Additionally, in the LGESS group, it is believed that the occurrence of these distinctions is contributed by the tumor having the smallest diameter, a low rate of poor-differentiated histological grade, a high rate of a low mitotic index, a low rate of ≥50% tumor necrosis, a low rate of positive lymphovascular invasion, and a positive lymph node status. In case the median OS was determined according to the FIGO stage, it was seen to be 87 (5-204) months for stage 1, 6 (6-6) months for stage 2, 106.5 (47-166) months for stage 3, and 36 (5-219) months for stage 4. There was no statistically significant difference between the groups. While perceived as a finding inconsistent with the existing literature, the diminished number of patients in stage II yielded a shorter survival duration than that observed in stage IV. Notably, stage IV exhibited the least survival.

The overall prognosis for the US is generally unfavorable, characterized by a variable recurrence rate that can range from 36%-63% (8,16,23-25). Similarly, recurrence was detected in 43.3% of the patients in our study. The most common recurrence location was in the lung (46.1%). The median time of recurrence was 23 months (3-219).

Our study possesses certain limitations, notably the rela-

tively small number of patients. The follow-up period for the patients could have been longer. Nevertheless, given the rarity of the US and the single-institution nature of the study, it is anticipated that this research will contribute valuable clinical insights to the limited body of literature on the US. Multicentric studies would be more valuable. Additionally, the rigorous inclusion and exclusion criteria employed in our study, while enhancing precision, have further constrained the overall number of patients.

In conclusion, the US are uncommon malignancies characterized by a poor prognosis, even in early stages, and are associated with a high recurrence ratio. The most effective treatment method remains unclear to date. Nonetheless, given the increased frequency of genetic mutations in uterine sarcoma and the recent progress made in targeted therapies, there is hope for potential enhancements in future treatment modalities.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of the Non-Interventional Clinical Research Ethics Committee, Dokuz Eylul University (Date: 14/12/2022, approval number: 2022/40-16). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: None

Authors' contribution: Concept: HBS., Design: HBS., OY. Data Collection or Processing: OY., KAM, Analysis, and Interpretation: OY., AA., Literature Search: SO., Writing: OY, KAM. Critical Review: HBS., OY., All authors read and approved the final manuscript.

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