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ORIGINAL ARTICLE

Prognostic and Predictive Factors for Uterine Sarcomas: A Single Center Experience

Uterus Sarkomlarında Prognostik ve Prediktif Faktörler: Tek Merkez Deneyimi

[1]Fazıl Avcı, [1]Belma Gözde Özdemir, [1]Mehmet Kulhan, [1]Ahmet Bilgi, [1]Cetin Celik

[1]Selcuk University Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Türkiye

Correspondence

Belma Gözde Özdemir, MD
Selcuk University Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Türkiye

E-Mail: gzdgrgn35@gmail.com

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ABSTRACT

Objective: To investigate the prognostic and predictive factors for uterine sarcomas, recognizing the challenge due to histological diversity and lack of definitive treatment.
Methods: We reviewed data from uterine sarcoma patients treated from July 2010 to August 2021. Cases were divided into endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and others (rhabdomyosarcoma, adenosarcoma), examining clinicopathological features, age, survival rates, and recurrence risk factors.
Results: In 43 patients (average age, 59.1 years), the most common symptom was vaginal bleeding. The majority were postmenopausal, with a breakdown of 65.1% ESS, 18.6% LMS, and 16.3% other sarcomas. Most (65.1%) were stage 1. Surgery was primarily via laparotomy (95.3%), with 79.1% receiving adjuvant therapy. Recurrence was 18.6%. Significant differences in survival rates were found across groups, with LMS significantly affecting survival and recurrence risk linked to tumor size and surgical stage. Five-year overall survival was 72.1%, and disease-free survival was 67.4%.
Conclusion: ESS is the most common uterine sarcoma, but LMS presents the worst prognosis. Tumor size and surgical stage are key to recurrence risk, highlighting the need for further study on adjuvant treatments.

Keywords: Gynecological surgery, predictive, prognostic factors, survival, uterine sarcoma

ÖZ

Amaç: Histolojik çeşitlilik ve kesin tedavi eksikliğinden kaynaklanan zorluğun farkındalığı ile uterus sarkomlarının prognostik ve prediktif faktörlerini araştırmayı amaçlandı.
Yöntemler: Temmuz 2010'dan Ağustos 2021'e kadar tedavi edilen uterus sarkomu hastalarından elde edilen veriler incelendi. Vakalar, klinikopatolojik özellikler, yaş, hayatta kalma oranları, ve tekrarlama risk faktörlerine göre sınıflandırıldı.
Bulgular: 43 hastada (ortalama yaş 59,1) en sık görülen semptom vajinal kanamaydı. Çoğunluk menopoz sonrası dönemdeydi ve %65,1 ESS, %18,6 LMS ve %16,3 diğer sarkomlardan oluşuyordu. Çoğu (%65,1) evre 1 idi. Cerrahi esas olarak laparotomi (%95,3) yoluyla yapıldı ve %79,1'i adjuvan tedavi aldı. Nüks oranı %18,6 idi. Gruplar arasında hayatta kalma oranlarında önemli farklılıklar bulundu; LMS, tümör boyutuna ve cerrahi aşamaya bağlı olarak hayatta kalma ve nüks riskini önemli ölçüde etkiliyor. Beş yıllık genel sağkalım %72,1, hastalıksız sağkalım ise %67,4 olarak belirlendi.
Sonuç: ESS en sık görülen uterin sarkomdur ancak LMS en kötü prognoza sahiptir. Tümör boyutu ve cerrahi evre, nüks riskinin önemli göstergesidir ve adjuvan tedaviler konusunda daha fazla çalışma yapılması ihtiyacı vurgulanmaktadır.

Anahtar Kelimeler: Jinekolojik cerrahi, prediktif, prognostik faktörler, sağkalım, uterus sarkomu

Introduction

Uterine sarcomas are rare mesenchymal tumors characterized by a poor prognosis, representing 3-4% of all malignant uterine cancers (1). In 2002, the World Health Organization (WHO) classified uterine sarcoma into three categories: carcinosarcoma (CS), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS) (2). However, in 2009, the diagnosis of carcinosarcoma was excluded from the uterine sarcoma classification, being redefined as type 2 endometrial cancer (3). As per the WHO's 2014 classification system, uterine sarcomas were divided into four subtypes: LMS, low-grade and high-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, and adenosarcoma (4). Among these,

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Complaints: geneltip@selcuk.edu.tr

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leiomyosarcoma, high-grade endometrial stromal sarcoma, undifferentiated sarcoma, and sarcomatous overgrowth adenosarcoma are associated with poor prognoses. In contrast, low-grade stromal sarcoma and adenosarcoma tend to have a more favorable prognosis (5).

The incidence of uterine sarcomas rises with age, ranging between 0.5 and 2.1 cases per 100,000 women (6, 7). They are most frequently diagnosed between the ages of 50 and 70, though the specific age of diagnosis can vary depending on the histological subtype (7, 8). Vaginal bleeding is a common symptom, yet there are no symptoms unique to sarcomas (9). In postmenopausal women who aren't on hormone replacement therapy, the presence of enlarging fibroids should prompt considerations of uterine sarcoma (10). These sarcomas are challenging to diagnose before surgery (11). Conventionally, the primary surgical treatment for uterine sarcomas is a total abdominal hysterectomy accompanied by bilateral salpingo-oophorectomy. The role of systemic lymph node dissection remains a topic of debate (12).

Histopathological diversity, an absence of definitive prognostic markers, rapid disease progression, high recurrence rates, and the potential for distant metastases define uterine sarcomas (13). One study found a recurrence rate of 30% for ESS and 60% for LMS, also noting that adjuvant chemotherapy neither reduced metastatic risk nor improved survival (11). While radiotherapy has been shown to enhance local control, it doesn't necessarily improve overall survival (14). Due to their propensity for early metastasis and recurrence, the overall 5-year survival rate for these sarcomas is often below 50%, signifying a grim prognosis (8, 15). Even now, the optimal treatment strategy for rare uterine sarcomas remains contentious. While surgery is the cornerstone of treatment, radiotherapy and chemotherapy serve as adjuvant treatments. In cases of metastatic or recurrent sarcomas, palliative treatments are employed (16). This study aims to investigate the prognostic and predictive factors for uterine sarcomas in a single center.

Materials and Methods

Ethical Consideration

The study received approval from the Selçuk University Ethics Committee on 04.10.2022, with the protocol number 2022/404.

Study Design

This retrospective study analyzed data from 43 patients diagnosed with uterine sarcoma who underwent surgery between July 2010 and August 2021. Based on prior classifications (3, 17), uterine sarcomas were categorized into three groups: endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and other sarcomas (including adenosarcoma and rhabdomyosarcoma). Cases diagnosed with uterine carcinosarcoma (CS) were excluded due to their removal from the uterine sarcoma classification in 2009 (3). Patients were staged according to the 2017 uterine sarcoma staging guidelines (18).

Inclusion and Exclusion Criteria

Included were patients with a histologic diagnosis of ESS, LMS, or other sarcoma subtypes, and those who underwent surgery specifically for sarcoma. Exclusion criteria comprised a CS diagnosis, cases deemed inoperable, and those with prior chemotherapy and/or radiotherapy treatment.

Data Collection

The following parameters were collected and analyzed: age, menopausal status (premenopausal or postmenopausal), gravida, parity, presenting symptoms (such as vaginal bleeding, palpable mass, rapid growth, or incidental findings), preoperative hemoglobin (Hb) level, neutrophil-to-lymphocyte ratio (NLR), type of surgical procedure, pathological tumor size, presence of myometrial invasion, omentum metastasis, presence of positive abdominal fluid, surgical stage (early stage being stages 1 and 2, and advanced stage being stages 3 and 4), type of adjuvant treatment (chemotherapy (CT) or radiotherapy (RT)), recurrence status, disease-free survival (DFS), and overall survival (OS). OS was measured from the date of diagnosis to the date of death or the last follow-up, whereas DFS was the duration from diagnosis to the emergence of recurrence. Regression analysis was performed for the risk of recurrence.

Surgical Procedure

All surgical procedures were carried out by a single experienced surgeon. Lymph node dissections were methodically executed, ranging from the pelvic region to the renal vein level. This encompassed bilateral dissections from the obturator, internal iliac, external iliac, common iliac, aortic bifurcation, aortocaval space, vena cava, and paraaortic areas, which were identified as left and right paraaortic areas respectively.

Statistical Analysis

SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Data (mean, median, standard deviation, and percentage) were calculated using Descriptive Tests. Pearson Chi-Square and Fisher's Exact Test were used for categorical parameters. In comparisons between groups, the Independent T-test and One-Way ANOVA test were used for continuous data with normal distribution, and the Whitney U Test and Kruskal-Wallis H test were used for data without normal distribution. Bonferroni correction was made for multiple comparisons. Kaplan-Meier method was used for survival times. Factors affecting survival times were evaluated using Binary Logistic regression analysis. A P value less than 0.05 was considered statistically significant.

Results

Among the 43 patients evaluated, the mean age was 59.1±2.8 years. No significant age difference was observed among ESS, LMS, and, Other sarcomas. The majority, 28 (65.1%), were diagnosed with endometrial stromal sarcoma (ESS), 8 (18.6%) with leiomyosarcoma (LMS), and 7 (16.3%) fell into the category of other sarcomas. At the time of diagnosis, 34 (79.0%) patients were postmenopausal, while 9 (21%) were premenopausal. Vaginal bleeding was the most common presenting complaint at presentation, reported in 55.8% of the cases (Table 1).

Laparotomy was the primary surgical approach, employed in 95.3% of the cases, with the remaining undergoing laparoscopy or vaginal surgery. In terms of disease staging, 28 (65.1%) were at stage 1, 4 (9.3%) at stage 2, 8 (18.6%) at stage 3, and 3 (7.0%) at stage 4. Recurrence was identified in 8 cases, which constitutes 18.6% of the patients (Table 1).

A significant majority, 34 patients (79.1%), received adjuvant treatment post-surgery. Upon comparing the treatment modalities among patients who only underwent surgery (9 cases), received

Table 1: Comparison of the characteristics of uterine sarcoma cases

	ESS (n=28)	LMS (n=8)	Others (n=7)	Total (n=43)	(%)	p-value	
Age (years)		59.1±14.5	58.0±10.0	60.4±9.4	59.1±2.8		0.938
Menopausal status							0.513
	Premenopause	8	1	0	9	21.0	
	Postmenopause	20	7	7	34	79.0	
Gravida		3 (2-13)	3.5 (3-5)	2 (2-5)	3 (2-13)		0.351
Parity		3 (0-12)	3.5 (3-5)	2 (2-5)	3 (0-12)		0.438
Complaint							0.583
	Bleeding	18	4	4	26	60.5	
	Mass	2	2	2	6	14.0	
	Rapid growth	2	0	0	2	4.7	
	Incidental	6	2	1	9	20.9	
Preoperative Hb		11.3±1.6	12.0±1.3	11.2±2.1	11.4±1.6		0.793
Preoperative NLR		11.7±7.4	12.2±5.7	14.3±11.0	12.2±7.6		0.741
Surgery method							0.333
	Laparoscopy	1	0	0	1	2.3	
	Laparotomy	27	8	6	41	95.3	
	Vaginal	0	0	1	1	2.3	
Surgery type							0.029
	TAH	0	1	0	1	2.3	
	VAH	0	0	1	1	2.3	
	TAH+ BSO± Omentectomy	4	4	0	8	18.6	
	TAH+ BSO PPLND± Omentectomy	22	3	6	31	72.1	
	Debulkıng	2	0	0	2	4.7	
Omentectomy							0.840
	Malign	1	0	1	2	10.5	
	Benign	11	3	3	17	89.5	
Myometrial Invasion							0.540

	No	10	3	6	19	44.2	
	Yes	18	5	1	24	55.8	
Tumor diameter, mm		78.5±38.6	87.4±78.4	62.1±42.5	77.5±48.0		0.597
Tumor diameter cut-off (5 cm)							0.762
	≤5 cm	9	2	3	14	32.6	
	>5 cm	19	6	4	29	67.4	
Tumor diameter cut-off (10 cm)							0.917
	≤10 cm	22	6	5	33	76.7	
	>10 cm	6	2	2	10	23.3	
Peritoneal fluid							0.381
	Malign	1	0	1	2	4.7	
	Benign	27	8	6	41	95.3	
Lymphadenectomy							0.019
	No	4	5	3	12	27.9	
	Yes	24	3	4	31	72.1	
Lymph node positivity							0.821
	No	21	3	5	29	93.5	
	Yes	2	0	0	2	6.5	
Stages							0.912
	1	18	5	5	28	65.1	
	2	2	1	1	4	9.3	
	3	6	1	1	8	18.6	
	4	2	1	0	3	7.0	
Surgical stage							0.719
	Early	20	6	6	32	74.4	
	Advanced	8	2	1	11	25.6	
Adjuvant treatment							0.229
	CT	13	2	3	18	41.9	
	RT	3	0	0	3	7.0	
	CT+RT	5	5	3	13	30.2	
	Expectant	7	1	1	9	20.9	
Recurrence							0.199
	No	22	6	7	35	81.4	
	Yes	6	2	0	8	18.6	
Localization of recurrence							0.729
	Local	3	-	-	3	37.5	
	Locoregional	3	-	-	3	37.5	
	Distant	-	2	-	2	25	
Recurrence treatment							0.617
	Chemotherapy	1	1	0	2	25	
	Surgery and chemot-herapy	4	1	0	5	62.5	
	Surgery. Chemotherapy and Radiotherapy	1	0	0	1	12.5	
Ex status							0.002*
	No	21	2	7	30	69.8	
	Yes	7	6	0	13	30.2	
DFS (months) mean (min-max)		52.8 (1-153)	31.6 (3 -140)	103.1 (10-154)			0.001*
OS (months) mean (min-max)		56.3 (1-153)	32.3 (3-140)	104.3 (10-154)			0.002*

+p<0.017 was considered statistically significant.

Hb: Hemoglobulin, NLR: Neutrophil to lymphocyte ratio, TAH: Total abdominal hysterectomy, VAH: Vaginal hysterectomy, BSO: Bilateral salpingo-oophorectomy, PPLND: Pelvic para-aortic lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, DFS: Disease-free survival, OS: Overall survival

radiotherapy (RT) post-surgery (3 cases), only received chemotherapy post-surgery (CT) (18 cases), and received both CT and RT post-surgery (13 cases), no statistically significant difference was found (p=0.199) (Table 1).

The total 5-year DFS and OS rates of the cases were calculated as 67.4% and 67.4%, respectively. A significant difference was evident between the groups in disease-free survival (DFS) and overall survival (OS) duration, with p-values of 0.001 and 0.002, respectively (Table 1, Figure 1, Figure 2). Regression analysis

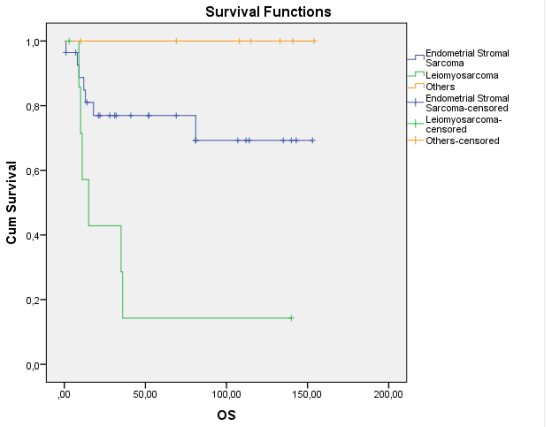

Figure 1. The effect of histologic types of uterine sarcoma cases on OS

indicated that the LMS histologic type was a significant risk factor influencing both DFS and OS (p=0.003 HR=6.155, 95% CI 1.871-20.250 and p=0.003 HR=6.075, 95% CI 1.846-19.996, respectively) (Table 2). Analyzing factors for recurrence, only tumor diameter showed statistical significance (p=0.04) (Table 3). Additionally, tumor diameter and surgical stage were significant factors for recurrence risk, with p-values of 0.033 and 0.022, respectively (Table 4). The overall 5-year OS was 72.1%, and DFS was 67.4%. ESS had a 5-year OS of 78.6% and a DFS of 71.4%, while LMS had both a 5-year OS and DFS of 25%.

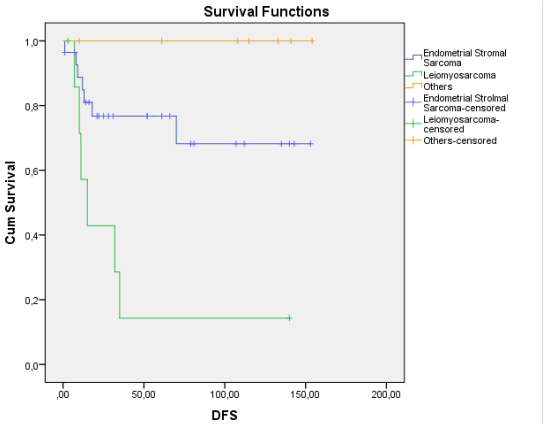

Figure 2. The effect of histologic types of uterine sarcoma cases on DFS

Discussion

Due to the histologic differences in uterine sarcomas, there isn't a widely accepted optimal treatment method. Traditionally, the management of these tumors entails a total abdominal hysterectomy coupled with a bilateral salpingo-oophorectomy. The predominant source of information on uterine sarcomas is based on extensive case series (5, 19, 20). In this study, we endeavor to share our clinical findings regarding the long-term outcomes of patients diagnosed with uterine sarcoma when a standardized management plan isn't available and to elucidate the factors that influence recurrence.

Table 2. Regression analysis of OS and DFS factors (-2 log Likelihood 78.944 p=0.045)

	OS				DFS			
Variables	*p*-value	HR	%95 CI		P value	HR	%95 CI	
NLR	0.950	1.003	0.916	1.098	0.998	1.000	0.913	1.095
Menopausal status	0.190	0.377	0.088	1.621	0.173	0.365	0.086	1.556
LMS vs others	0.003*	6.155	1.871	20.250	0.003*	6.075	1.846	19.996
Early vs advanced	0.609	0.686	0.161	2.913	0.651	0.716	0.169	3.038
Adjuvant treatment	0.236	3.158	0.472	21.140	0.278	2.821	0.432	18.400
Presence of recurrence	0.783	1.212	0.308	4.776	0.913	1.079	0.275	4.240

*p<0.05 was considered statistically significant. CI: Confidence interval, DFS: Disease-free survival, HR: Hazard ratio,

NLR: neutrophil to lymphocyte ratio, LMS: leiomyosarcoma, OS: Overall survival

Vaginal bleeding, a prevalent symptom associated with uterine sarcomas, has been reported in 25% to 92% of cases across various studies (1, 7, 16, 21, 22). In our cohort, this symptom was identified in 60.5% of patients. Typically, these malignancies are diagnosed at a more advanced age (8, 15, 16). The age of diagnosis also differs according to the histologic subtype, with studies suggesting an earlier onset for

Table 3: Comparison of uterine sarcoma cases in terms of recurrence

Variables		Recurrence Yes (n=8)	(%)	Recurrence No (n=35)	(%)	Total (n=43)	(%)	*p*-value
Age (years)		57.0±15.7		59.6±12.3				0.988
Menopausal status								0.541
	Premenopause	2	25.0	7	20.0	9	20.9	
	Postmenopause	6	75.0	28	80.0	34	79.1	
Parity		3 (2-7)		3 (0-12)				0.930
NLR		8.3±5.3		12.1±8.1				0.947
Omentectomy								0.795
	Malign	0	0	2	11.8	2	10.5	
	Benign	2	100.0	15	88.2	17	89.5	
Myometrial Invasion								0.493
	No	3	37.5	16	45.7	19	44.2	
	Yes	5	62.5	19	54.3	24	55.8	
Tumor diameter (mm)		88.1±41.0		70.4±39.3		108. 7±70.2		0.040
Tumor diameter cut-off (5 cm)								0.180
	≤5 cm	1	12.5	13	37.1	14	32.6	
	>5 cm	7	87.5	22	62.9	29	67.4	
Tumor diameter cut-off (10 cm)								0.610
	≤10 cm	6	75.0	27	77.1			
	>10 cm	2	25.0	8	22.9			
Peritoneal fluid								0.659
	Malign	-	-	2	5.7	2	4.7	
	Benign	8	100	33	94.3	41	95.3	
Lymph node positivity								0.645
	No	6	100	23	92.0	29	93.5	
	Yes	0	0	2	8.0	2	6.5	
Stages								0.137
	1	4	50.0	24	68.6	28	65.1	
	2	0	0	4	11.4	4	9.3	
	3	2	25.0	6	17.1	8	18.6	
	4	2	25.0	1	2.9	3	70	
Surgical stage								0.099
	Early	4	50.0	28	80.0	32	74.4	
	Advanced	4	50.0	7	20.0	11	25.6	
LMS *vs* others								0.467
	LMS	2	25.0	6	17.1	8	18.6	
	Others	6	75.0	29	82.9	35	81.4	
Ex status								0.458
	No	5	62.5	25	71.4	30	69.8	
	Yes	3	37.5	10	28.6	13	30.2	
Adjuvant treatment								0.207
	No	3	37.5	6	17.1	9	20.9	
	Yes	5	62.5	29	82.9	34	79.1	
DFS (months)		59.1±9.5 (84.1-127.0)		108.0±12.1 (84.3-131.6)				0.837
OS (months)		81.7±14.6 (53.2-110.8)		108.0±12.1 (84.3-131.6)				0.945

*p<0.05 was considered statistically significant.

NLR: Neutrophil-lymphocyte ratio, LMS: Leiomyosarcoma, DFS: Disease-free survival, OS: Overall survival

both ESS and LMS (7, 16, 22). Our findings are consistent with this, showing a mean diagnosis age of 59.1 years. A key distinction of our study from others is the exclusion of carcinosarcoma (CS) cases. Laparotomy remains the preferred surgical approach. Our results, with a significant 95.3% of patients undergoing laparotomy,

Table 4: Regression analysis of factors for recurrence (Sensitivity of the test, 88.4% and p=0.03 -2Log likelihood 25.810 Nagelkerke R Square=0.49)

Variables	*p*-value	HR	%95 CI	
Age (years)	0.324	0.932	0.810	1.072
NLR	0.334	0.923	0.784	1.086
Tumor diameter (mm)	0.033*	1.028	1.002	1.055
Menopausal status	0.427	4.591	0.107	196.507
LMS vs others	0.622	0.475	0.025	9.106
Early vs others	0.022*	61.565	1.804	2101.347
Adjuvant treatment	0.109	0.080	0.004	1.748

*p<0.05 was considered statistically significant. CI: Confidence interval,

NLR: Neutrophil to lymphocyte ratio, LMS: Leiomyosarcoma, HR: Hazard ratio

align with previous findings (16, 23). The rate of LMS detection in other studies varies between 40% and 83.6% (7, 8, 15, 22, 24). In our sample, 65.1% of the cases were diagnosed as ESS, followed by LMS at 18.6%, and other sarcomas at 16.3%. A significant feature of our patient group, diverging from some other studies, is the majority being diagnosed at an early stage (16, 21-23).

The hormone-sensitive nature of ESS mandates consideration for bilateral salpingo-oophorectomy, even during the premenopausal stage in stage 1 (7). In the meta-analysis by Rossini et al., it was suggested that ovarian tissue could be preserved in premenopausal patients even if there was a consensus on BSO in menopausal patients. However, there was insufficient evidence in the literature to recommend this procedure (25). In our patient pool, this procedure was also performed on premenopausal ESS patients, resulting in a total of 41 cases (90.7%) undergoing BSO.

The utility of lymph node dissection in uterine sarcomas remains contentious (12). In this study, lymphadenectomy was performed in 72.1%. Lymphadenectomy was performed most frequently in the ESS group and least frequently in the LMS group. While some studies highlight the advantages of postoperative radiotherapy, others suggest that adjuvant treatments don't considerably alter the disease progression (16, 26). In our study, 79.1% of the patients underwent some form of adjuvant treatment. Recurrence rates, as highlighted in previous research, fluctuate between 22% and 70% (8, 11, 21, 27, 28). Our study indicated a recurrence rate of 18%, with the majority being locoregional.

Regarding prognostic factors, the literature yields mixed results. Variables such as age, menopausal status, tumor stage, tumor size, and histological type have been pinpointed as crucial to overall survival in some studies (22, 23, 27-31). In contrast, our findings identify LMS histology as the only prognostic factor for survival. Tumor histologic type and size emerged as significant influencers of survival outcomes. The role of inflammatory cells surrounding cancer tissues in determining cancer progression and prognosis is pivotal (32). High preoperative NLR was shown to be an independent prognostic marker for predicting poor prognosis in soft tissue sarcoma (33, 34). Yet, our analysis showed that the preoperative neutrophil-lymphocyte ratio (NLR) didn't significantly correlate with survival.

There is still no standard approach to the management of uterine sarcomas today. Because uterine sarcomas are both a heterogeneous group and their diagnosis is histopathological. Therefore, factors that can be used or predicted in the preoperative diagnosis of uterine sarcoma are being investigated. However, the studies conducted are retrospective. There are still no prospective studies on this subject. In this study, lymphadenectomy and surgical procedure were significant factors for ESS, LMS, and other sarcoma groups, while only histological type was found to be a significant factor in regression analysis. When the cases were evaluated in terms of recurrence, only the tumor diameter at the time of diagnosis was found to be a significant factor. In other words, as the tumor diameter increases, the risk of recurrence also increases. In this study, no cut-off value was found for tumor diameter recurrence. Studies with more cases are needed to explain the relationship between tumor diameter and recurrence.

This study's constraints encompass its retrospective design, its single-center scope, and the limited number of cases. However, it offers valuable insights by presenting the clinical features and long-term outcomes of patients diagnosed with uterine sarcoma,

emphasizing factors affecting recurrence, and deliberately excluding carcinosarcoma diagnoses.

Conclusions

The predominant histologic subtype of uterine sarcoma is endometrial stromal sarcoma. Leiomyosarcoma is the subtype associated with the most adverse prognosis. Tumor size and surgical stage are the most critical determinants of recurrence rates in uterine sarcomas. Although early surgical intervention is effective in the management of sarcomas, additional research is urgently needed to determine the benefits of adjuvant therapies.

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